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

Robert Epstein, M.D.

Marc Chioda, Pharm.D.

Touchpoints

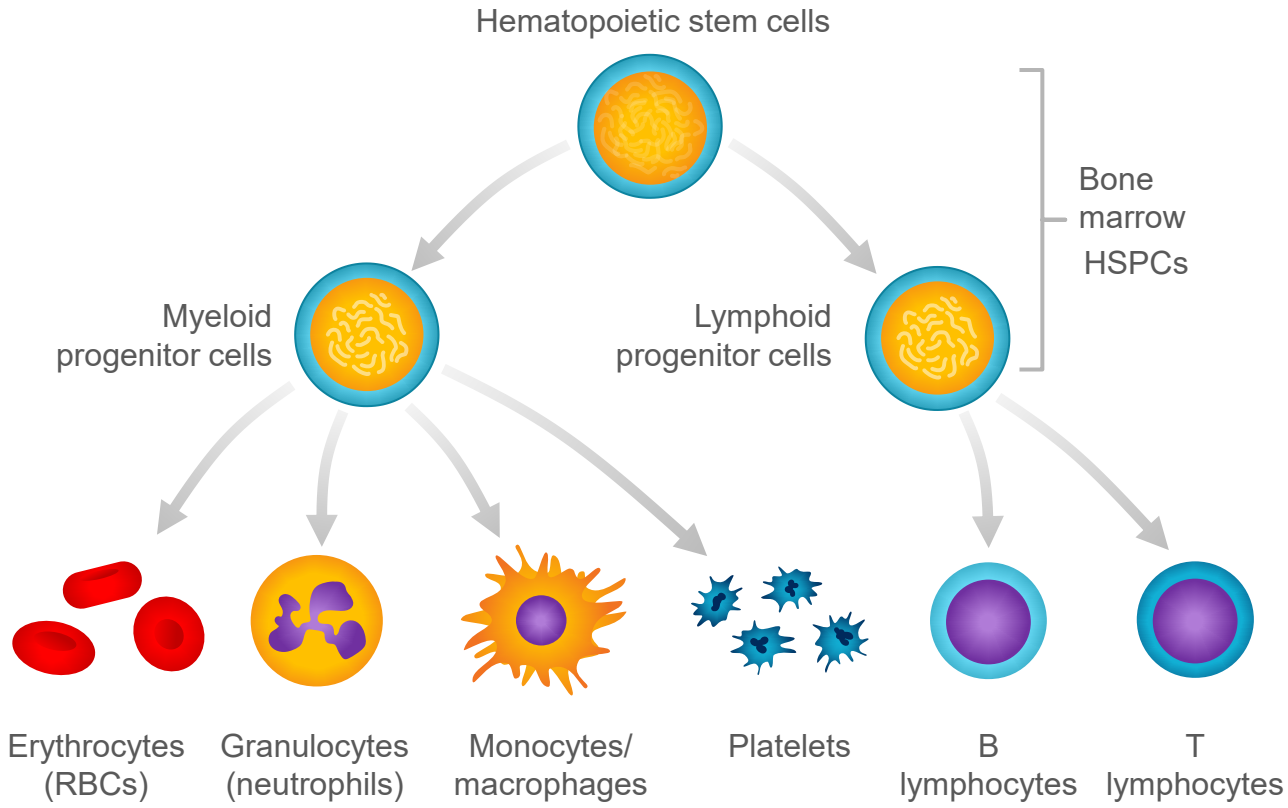
- Chemotherapy-induced myelosuppression (CIM) today and beyond
- Current therapies and clinical recommendations for managing CIM
- Health economic & patient-reported experience
  - Redefining the real-world impact of CIM
- Investigational therapies focused on the root of the problem

G1 THERAPEUTICS

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



Villines Z. What to know about hematopoiesis. Available at: https://www.medicalnewstoday.com/articles/319544.php (Accessed Aug 10, 2020).

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

1. Javarappa KK, et al. *SLAS Discov*. 2018;23:687-696. **2.** He S, et al. *Sci Transl Med*. 2017;9(387):eaal3986. doi:10.1126/scitranslmed.aal3986. **3**. Lyman G. Cancer Network. Available at: https://www.cancernetwork.com/ovarian-cancer/risk-assessment-oncology-clinical-practice. Accessed 5/18/2020.

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]

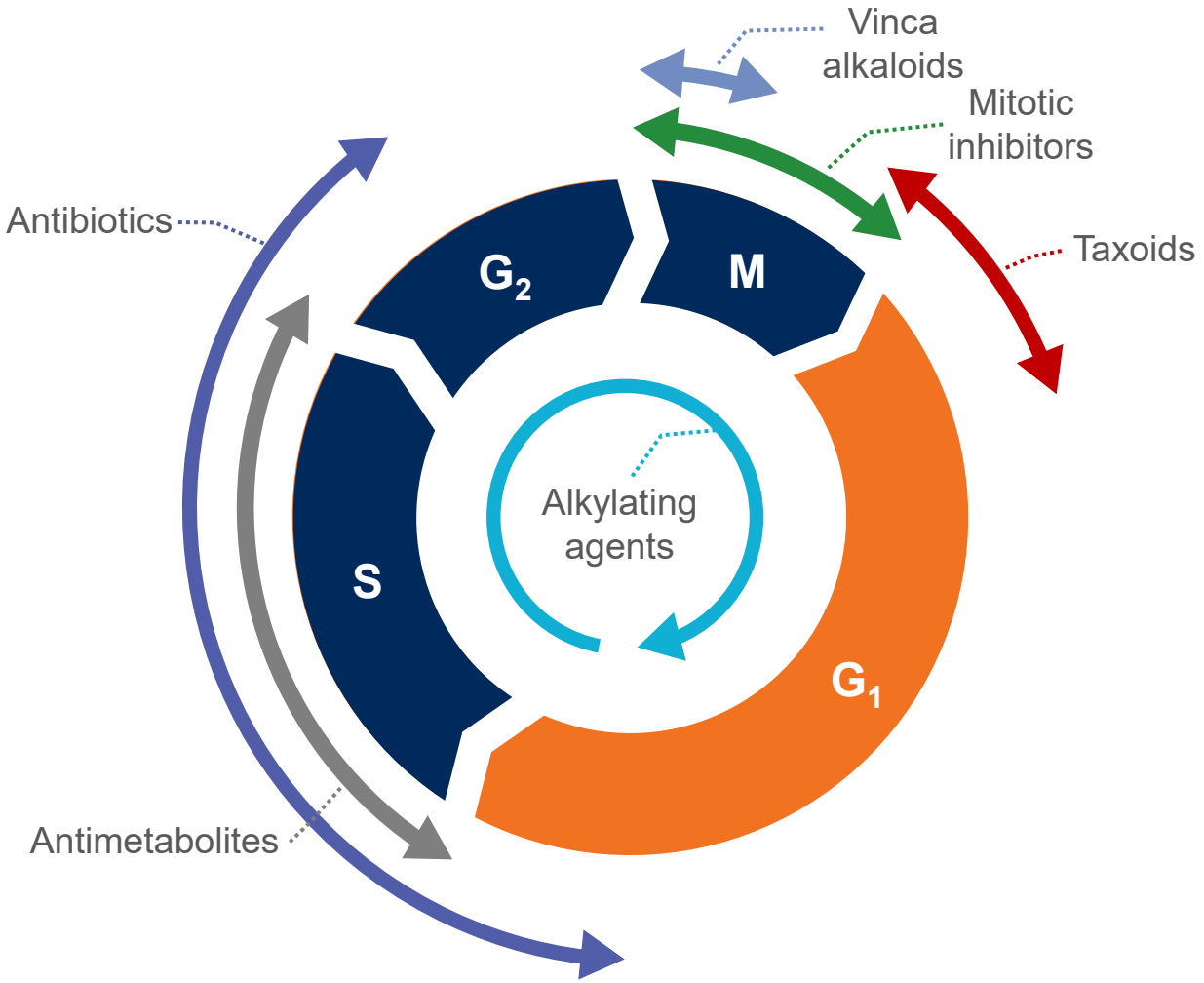
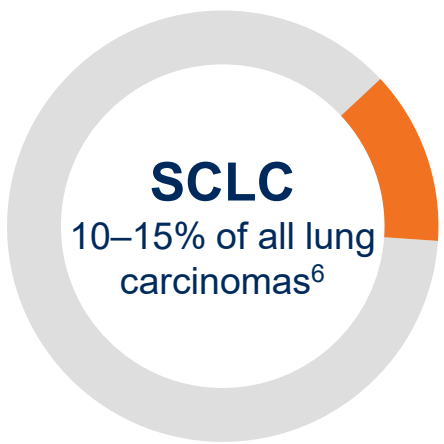


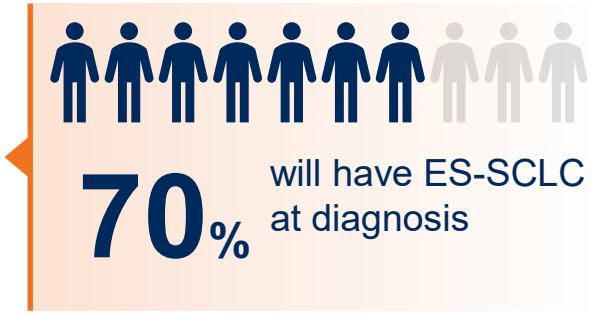
Figure adapted from: http://chemoth.com/cellcycle.

1. The cell reproductive cycle and cytotoxic drugs. Available at: http://chemoth.com/cellcycle (Accessed Aug 10, 2020). **2.** Huang C-Y, et al. *Biomedicine.* 2017;7:23.

Chemotherapy remains the cornerstone of treatment for patients with SCLC

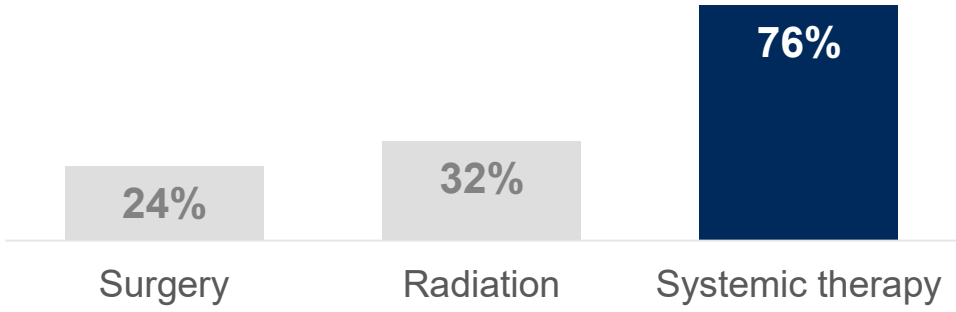
- Lung cancer is the leading cause of cancer-related death in the US and around the world[1]
- SCLC accounts for ~13% of all lung cancer cases in the US, with most patients diagnosed at an advanced stage[2,3]
- Prognosis is poor, with a 5-year survival rate of 6%, decreasing to 3% among patients with distant metastasis[2]
- Systemic chemotherapy, alone or in combination with immune checkpoint inhibitors, is the standard of care for patients with advanced SCLC[4]





Standard-of-care chemotherapy regimens for SCLC present a treatment challenge due to clinically significant, multilineage myelosuppression[5]

Treatment for patients with ES-SCLC[8]



1. American Cancer Society. Key statistics for lung cancer. Available at: https://www.cancer.org/cancer/lung-cancer/about/key-statistics.html (Accessed Jul 15, 2020). **2.** American Society of Clinical Oncology. Lung cancer - small cell: statistics. Available at: https://www.cancer.net/cancer-types/lung-cancer-small-cell/statistics (Accessed Jul 15, 2020). **3.** American Society of Clinical Oncology. Lung cancer - small cell: stages. Available at: https://www.cancer.net/cancer-types/lung-cancer-small-cell/stages (Accessed Jul 15, 2020). 4. American Cancer Society. Treatment choices for small cell lung cancer, by stage. Available at: https://www.cancer.org/cancer/lung-cancer/treating-small-cell/by-stage.html (Accessed Jul 27, 2020). **5.** Kurtin S. *J Adv Pract Oncol.* 2012;3:209–24. **6.** Govindan R, et al. *J Clin Oncol.* 2006;24:4539–44. **7.** Byers LA, Rudin CM. *Cancer.* 2015;121:664–72. **8.** Kantar Health. Small cell lung cancer v1.1. 2019.

G1 THERAPEUTICS

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]

	1L SCLC incidence of Grade 3/4[6]	2L SCLC incidence of Grade 3/4[7]	Current treatment	Unmet need/burden
Neutropenia (fewer neutrophils)	23%	54% (3% FN)	G-CSF rescue	~70% bone pain (~25% severe)[9] induced by G-CSFs (severe pain treated with NSAIDs, antihistamines, and opioids)
Anemia (fewer red blood cells)	14%	31%	ESA rescue, transfusion rescue	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]
Thrombocytopenia (fewer platelets)	10%	54%	Transfusion rescue	No options other than transfusions[4]

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

1. Taylor SJ, et al. *Sci Transl Med*. 2017;9:eaam8060. **2.** Crawford J, et al. *Cancer*. 2004;100:228–37. **3.** Groopman JE, Itri LM. *J Natl Cancer Inst*. 1999;91:1616–34.
4. Kuter DJ. *Oncology (Williston Park)*. 2015;29:282–94. **5.** Lyman GH. *Oncology (Williston Park)*. 2006;20:16–25. **6.** Horn L, et al. *N Engl J Med*. 2018;379:2220–9. **7.** von Pawel J, et al. *J Clin Oncol*. 2014;32:4012–9. **8.** Epstein R, et al. *J Clin Oncol*. 2020;38(15_suppl):Abstract #e19300. **9.** Kirshner JJ, et al. *J Clin Oncol*. 2012;30:1974–9.
10. Information on ESA epoetin alfa (marketed as Procrit, Epogen), darbepoetin alfa (marketed as Aranesp). Available at: https://www.fda.gov/drugs/postmarket-drug-safety-information-patients-and-providers/information-erythropoiesis-stimulating-agents-esa-epoetin-alfa-marketed-procrit-epogen-darbepoetin (Accessed Apr 2, 2020).

G1 THERAPEUTICS

Chemotherapy-Induced Neutropenia (CIN)

- Common yet serious adverse event (AE) following myelosuppressive chemotherapy[1]
- Risk factors can be[2]
  - Patient specific
  - Disease specific
  - Treatment specific
- Absolute neutrophil count (ANC) <1,000/µL; clinically significant when ANC is <500/µL[1]
  - 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[4]

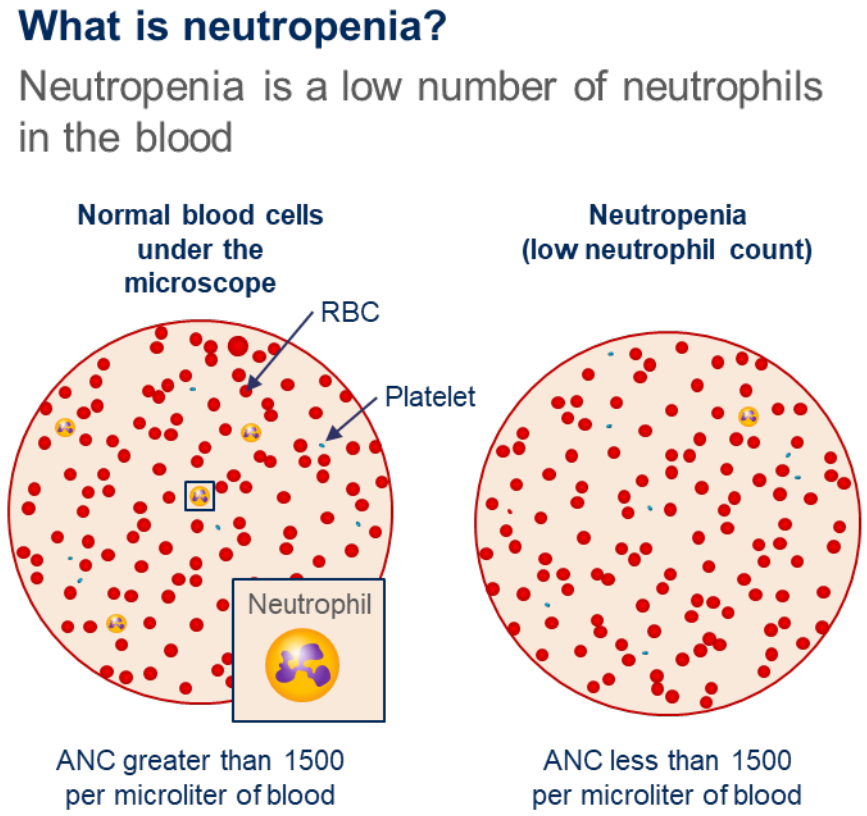
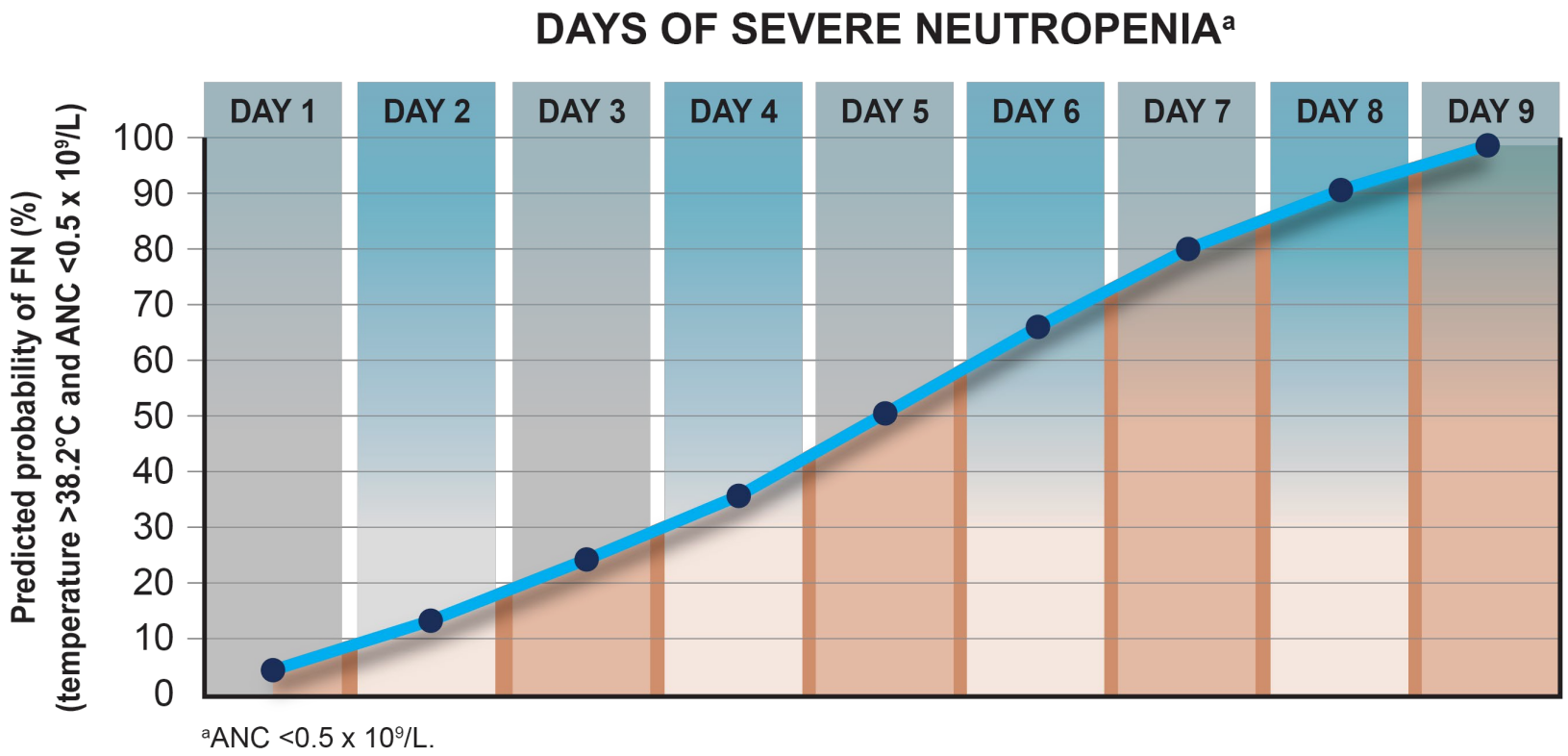


Figure adapted from: https://jamanetwork.com/journals/jamaoncology/fullarticle/2645851.

- **1.** Bond CT, et al. *J Oncol Pharm Practice*. 2018;24:412-423. **2.** Lyman GH, et al. *The Oncologist*. 2005;10:427-437. **3.** National Comprehensive Cancer Network. Hematopoietic Growth Factors (Version 2.2020). Available at: https://www.nccn.org/professionals/physician_gls/pdf/growthfactors.pdf. Accessed August 11, 2020. **4.** Trautman H, et al. *J Manag Care Spec Pharm*. 2019;25:94-101. **5.** Horn L, et al. *N Engl J Med.* 2018;379:2220-2229.

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



[a]ANC <0.5 x 10^9/L.

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

Adapted from Blackwell S, Crawford J. Filgrastim (r-metHuG-CSF) in the chemotherapy setting. In: Morstyn G, Dexter TM. Filgrastim (r-metHuG-CSF) in Clinical Practice. New York, NY: Marcel Dekker; 1994:103–116.

G1 THERAPEUTICS

1. 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. **2.** Trautman H, et al. *J Manag Care Spec Pharm*. 2019;25:94-101.

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

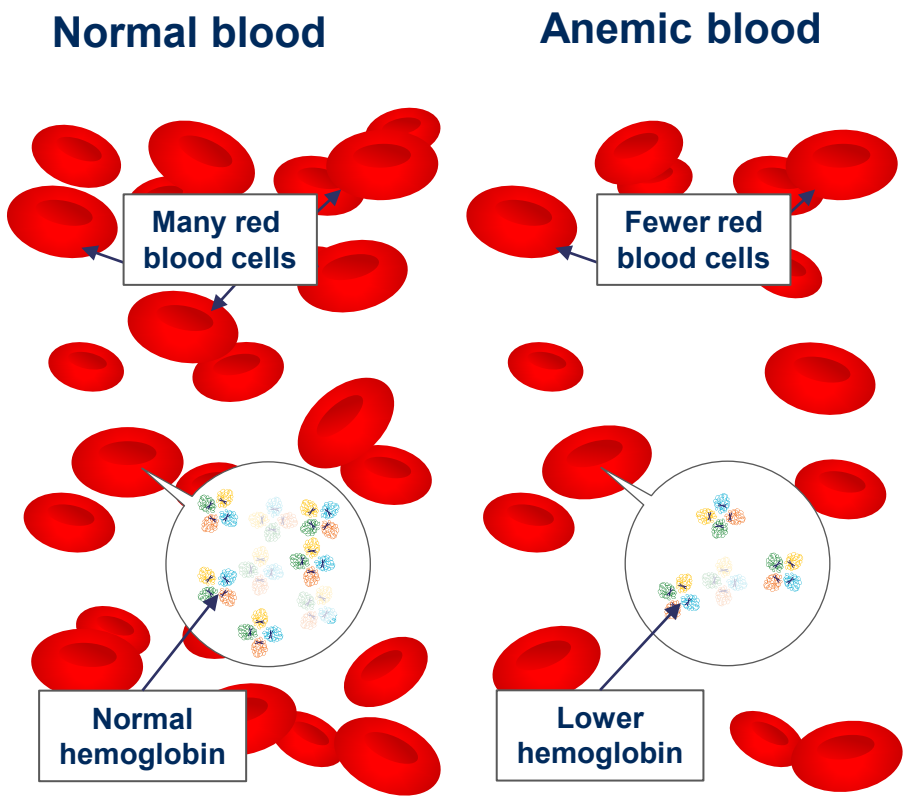
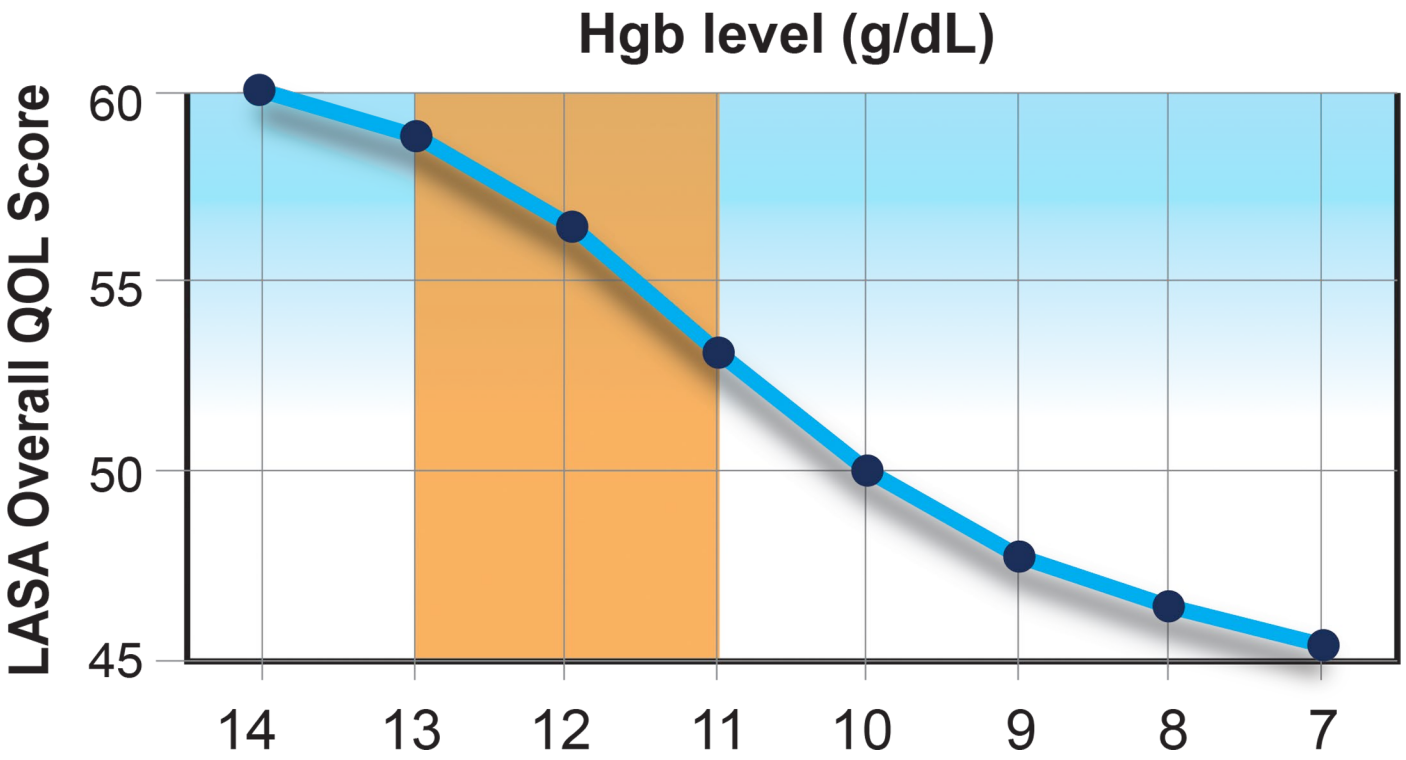


Figure adapted from:
https://www.aboutkidshealth.ca/Article?contentid=841&language=English.

- **1.** National Comprehensive Cancer Network. Hematopoietic Growth Factors (Version 2.2020). Available at: https://www.nccn.org/professionals/physician_gls/pdf/growthfactors.pdf. Accessed August 11, 2020. **2.** Xu H, et al. *Clin Epidemiol*. 2016;8:61-71.

Hemoglobin Level is Associated with QoL

- CIA can cause[1,2]
  - fatigue
  - pale skin
  - dyspnea
  - drowsiness
  - depression
  - tachycardia
  - dizziness
- Consequences of CIA can lead to chemotherapy delays and a negative effect on QoL[1,3]
- CIA is associated with increased morbidity, mortality, and healthcare costs[1]



Abbreviations: Hgb, hemoglobin; LASA, Linear Analog Scale Assessment; QOL, quality of life.

1. Xu H, et al. *Clin Epidemiol*. 2016;8:61-71. **2.** Crawford J, et al. *Cancer*. 2002;95:888-895. 3. Bryer E, et al. *International Journal of Clinical Transfusion Medicine*. 2018;6:21-31. Available at: https://doi.org/10.2147/IJCTM.S187569. Accessed 6/8/2020.

Chemotherapy-Induced Thrombocytopenia (CIT)

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

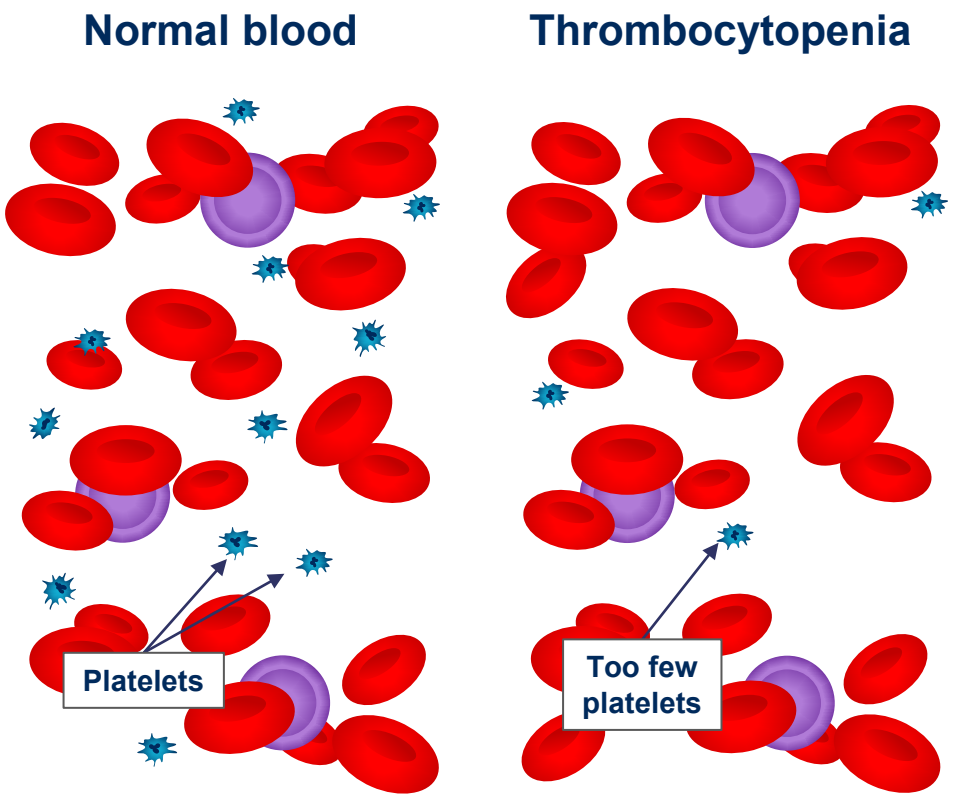
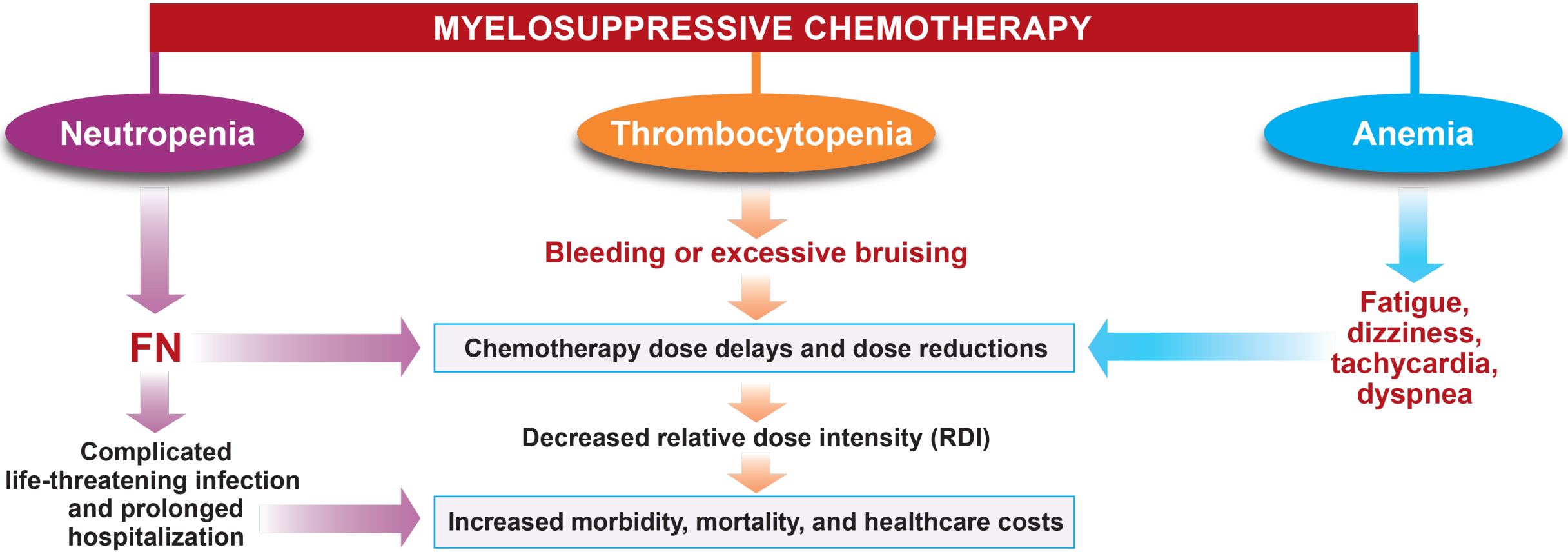


Figure adapted from: https://www.fairview.org/sitecore/content/Fairview/Home/Patient-Education/Articles/English/t/h/r/o/m/Thrombocytopenia_40932.

- **1.** Weycker D, et al. *BMC Cancer*. 2019;19:151. **2.** Kuter DJ. *Oncology* (Williston Park).2015;29:282-294. **3.** Soff GA, et al. *J Clin Oncol*. 2019;37(15_suppl). Abstr 1555. **4.** Zhang X, et al. *Cochrane Database Syst Rev*. 2017;11:CD012035. **5.** Soff GA, et al. *J Clin Oncol.* 2019;37:2892-2898.

Consequences of Myelosuppressive Chemotherapy

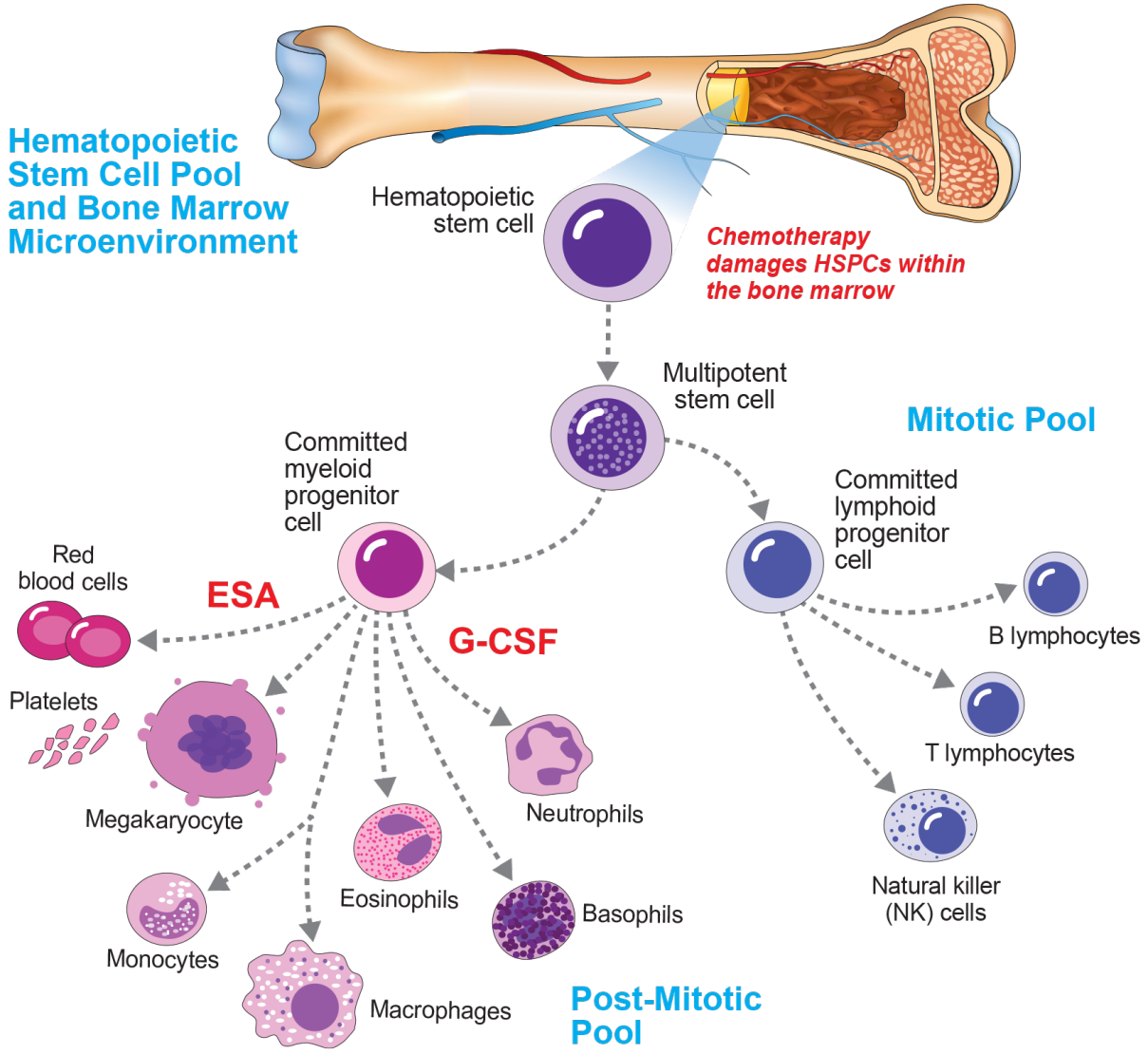


Abbreviations: FN, febrile neutropenia.

Current therapies and clinical recommendations for managing CIM

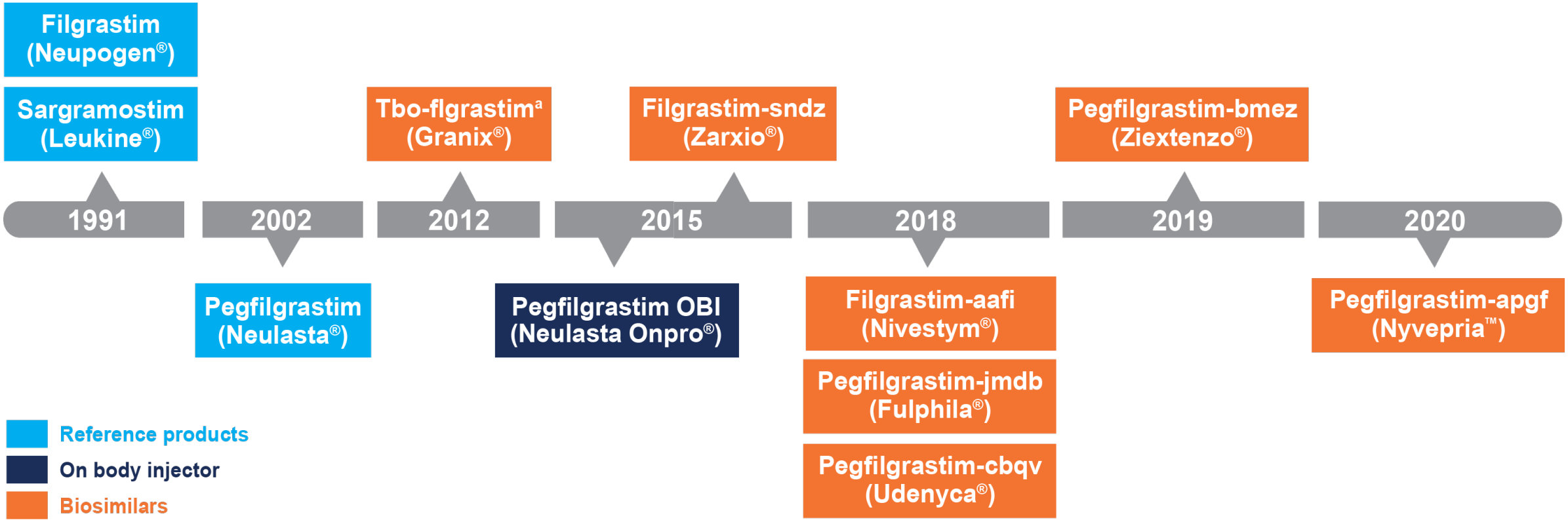
Hematopoietic Rescue Therapies for Chemotherapy-Induced Myelosuppression

- 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.

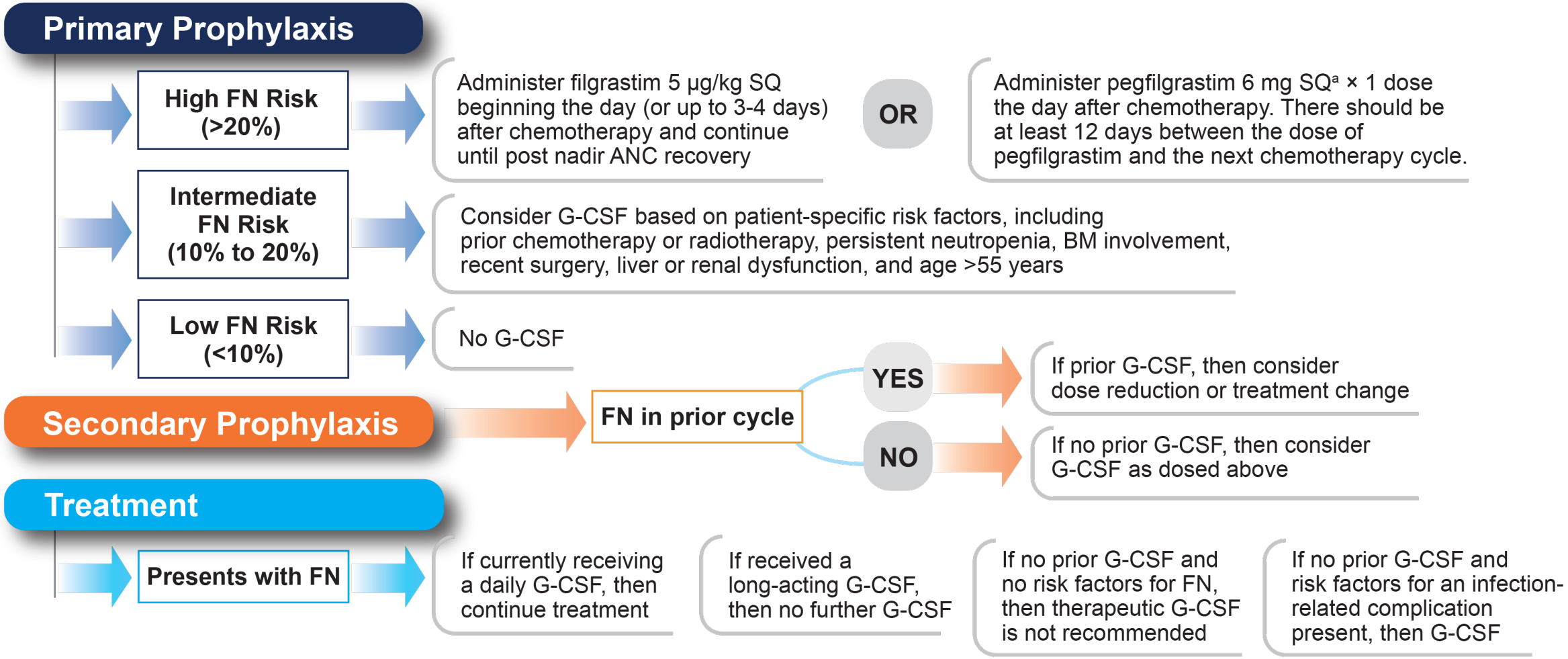
FDA-Approved WBC Growth Factors



Abbreviations: OBI, on-body injector; WBC, white blood cell.
[a]Tbo-filgrastim approval in 2012 was before implementation of the FDA's biosimilar approval process.
FDA-approved drugs. Available at: https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=BasicSearch.process. Accessed 5/1/2020.

G1 THERAPEUTICS

NCCN Recommendations for G-CSF

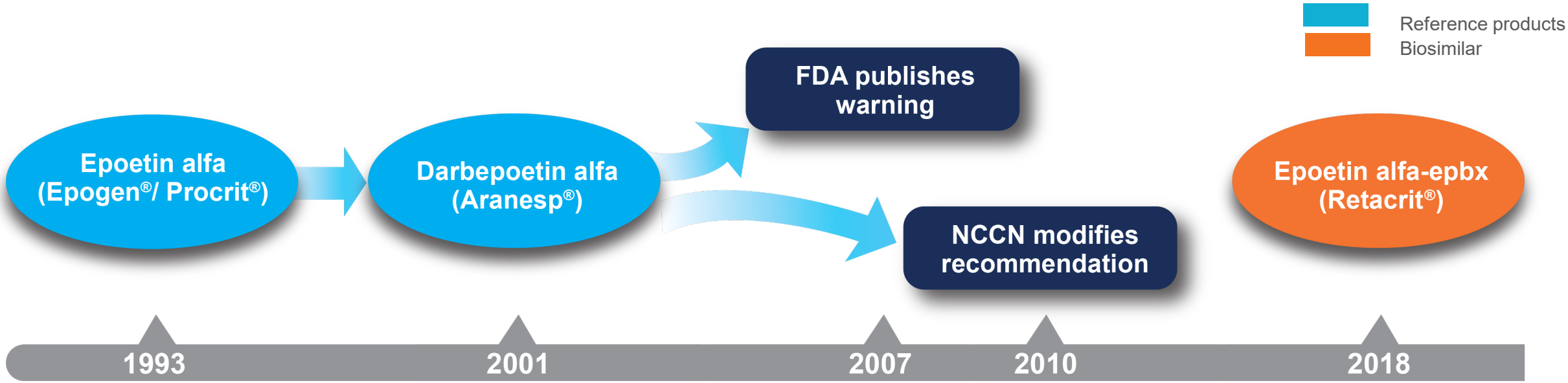


Abbreviations: ANC, absolute neutrophil count; BM, bone marrow; FN, febrile neutropenia; G-CSF, granulocyte colony-stimulating factor; NCCN, National Comprehensive Cancer Network; SQ, subcutaneous.

[a]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.

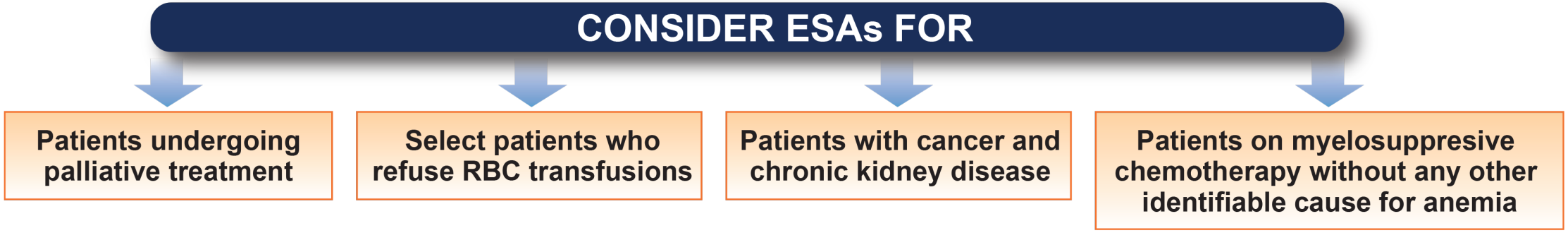
FDA-Approved Erythropoiesis Stimulating Agents



Abbreviations: FDA, Food and Drug Administration; NCCN, National Comprehensive Cancer Network.

Abdel-Razeq H, et al. *Crit Rev Oncol Hematol*. 2020;145:102837.

NCCN Recommendations for ESAs



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

Abbreviations: ESA, erythropoiesis-stimulating agent; NCCN, National Comprehensive Cancer Network.

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Hematopoietic Growth Factors V.1.2020. © National Comprehensive Cancer Network, Inc. 2019. All rights reserved. To view the most recent and complete version of the guidelines, go online to NCCN.org.

G1 THERAPEUTICS

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 $<10 \times 10^9$/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

G1 THERAPEUTICS

Abbreviations: ASCO, American Society of Clinical Oncology.

Schiffer CA, et al. *J Clin Oncol*. 2017;36:283-299.

NCCN Temporary Hematopoietic Growth Factors: COVID-19 Specific Recommendations

	Recommendation
Chemotherapy-Induced Neutropenia	Expand primary prophylactic use of G-CSF to minimize risk of FN • Revised threshold for use of G-CSF from use with only high-risk regimens (>20%) to intermediate-risk (10%−20%) or high-risk regimens • 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 • Consider using G-CSF to accelerate post-HCT recovery to minimize days of hospitalization • Consider self administration or use of on-body injector to minimize visits to outpatient center • Avoid G-CSF in case of respiratory infection, respiratory symptoms, or confirmed or suspected COVID-19
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 × 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 × 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.

NCCN Hematopoietic Growth Factors Short Term Recommendations Specific to Issues with COVID-19 (SARS-CoV-2). Available at: https://www.nccn.org/covid-19/pdf/HGF_COVID-19.pdf.

G1 THERAPEUTICS

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

G1 THERAPEUTICS

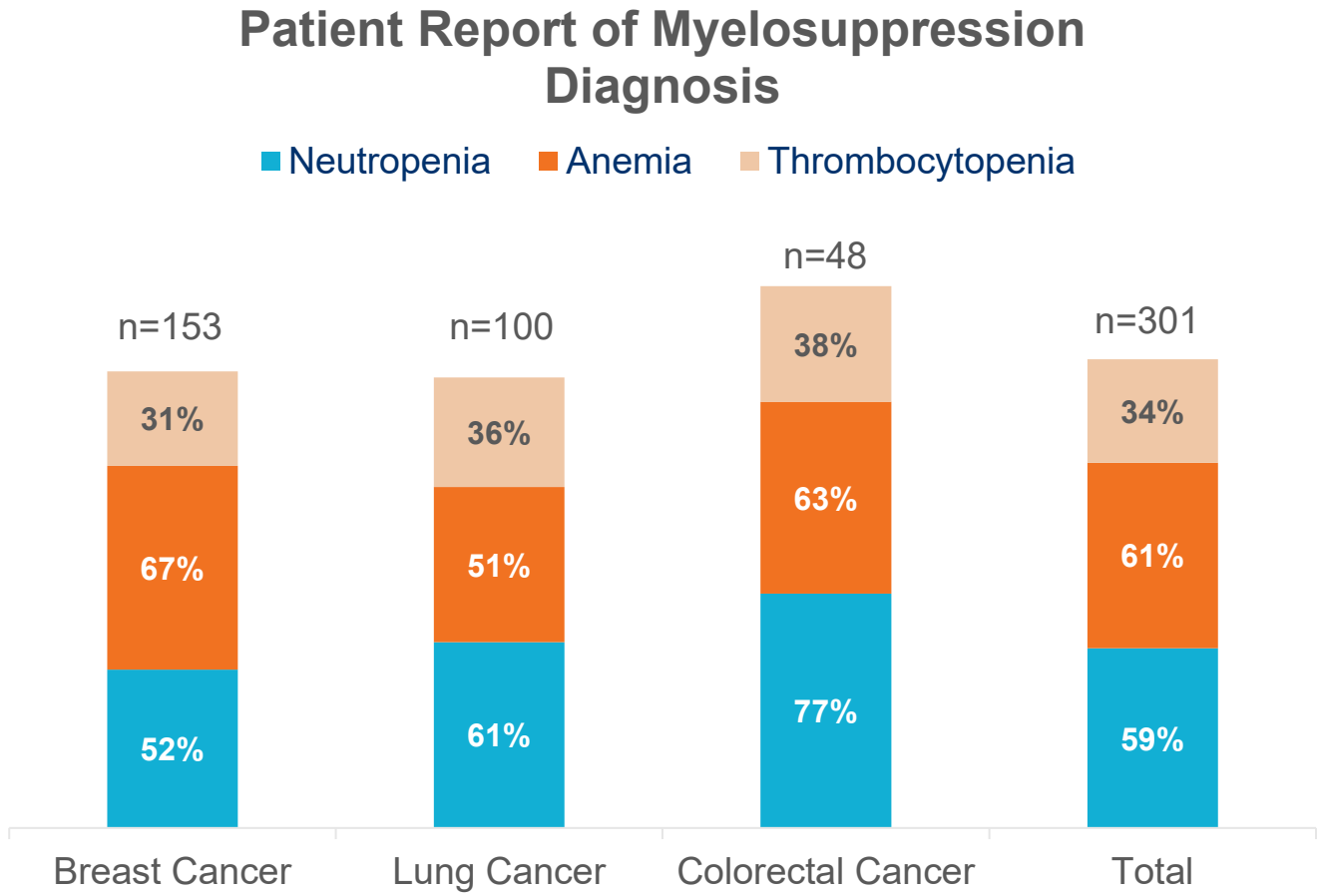
Abbreviations: ESA, erythropoiesis-stimulating agent; G-CSF, granulocyte colony-stimulating factor.

Health economic & patient-reported experience

— Redefining the real-world impact of CIM

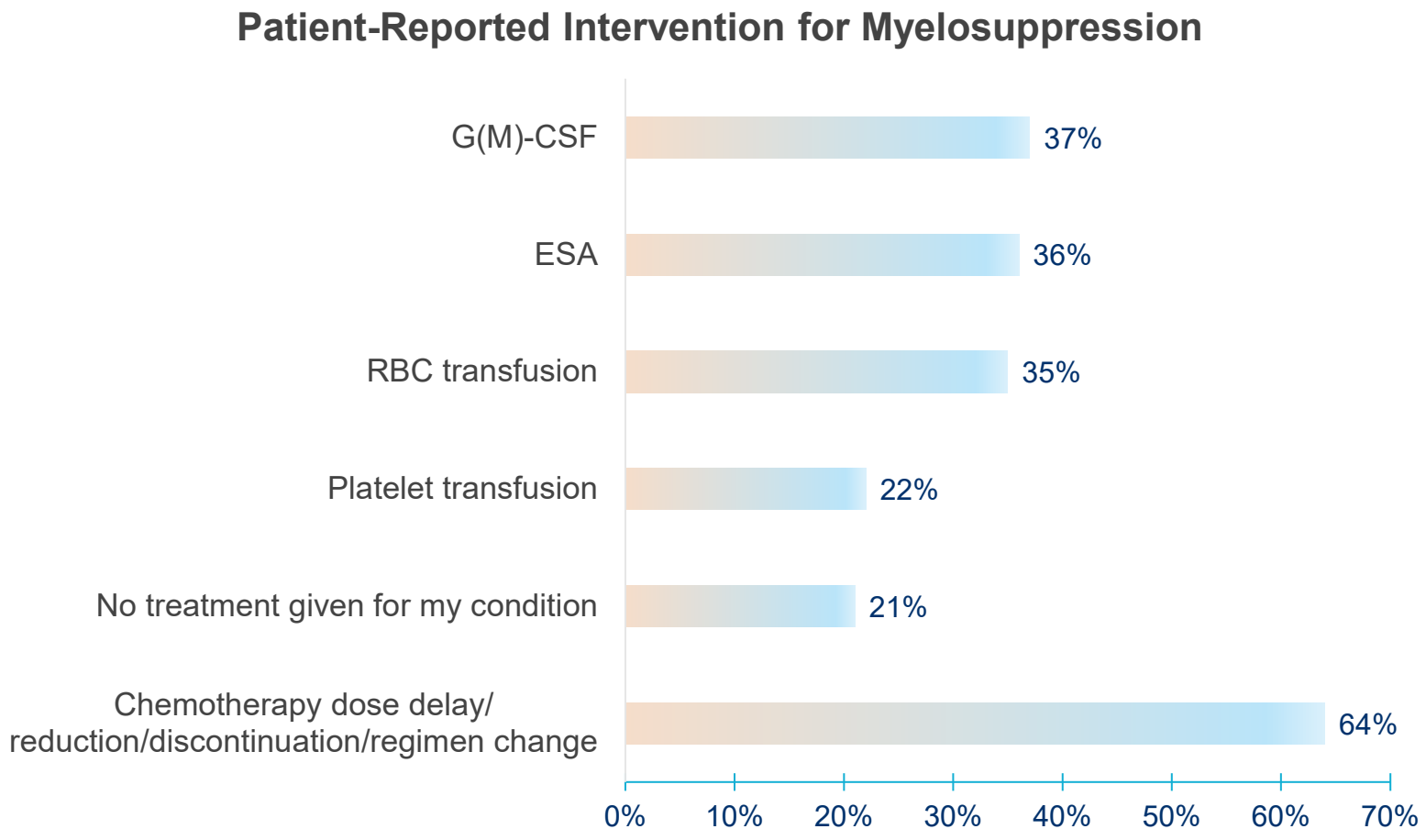
Real-World Management of Chemotherapy-Induced Myelosuppression

- 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



Epstein RS, et al. *Adv Ther*. 2020; epub online July 8, 2020.

Real-World Management of Chemotherapy-Induced Myelosuppression

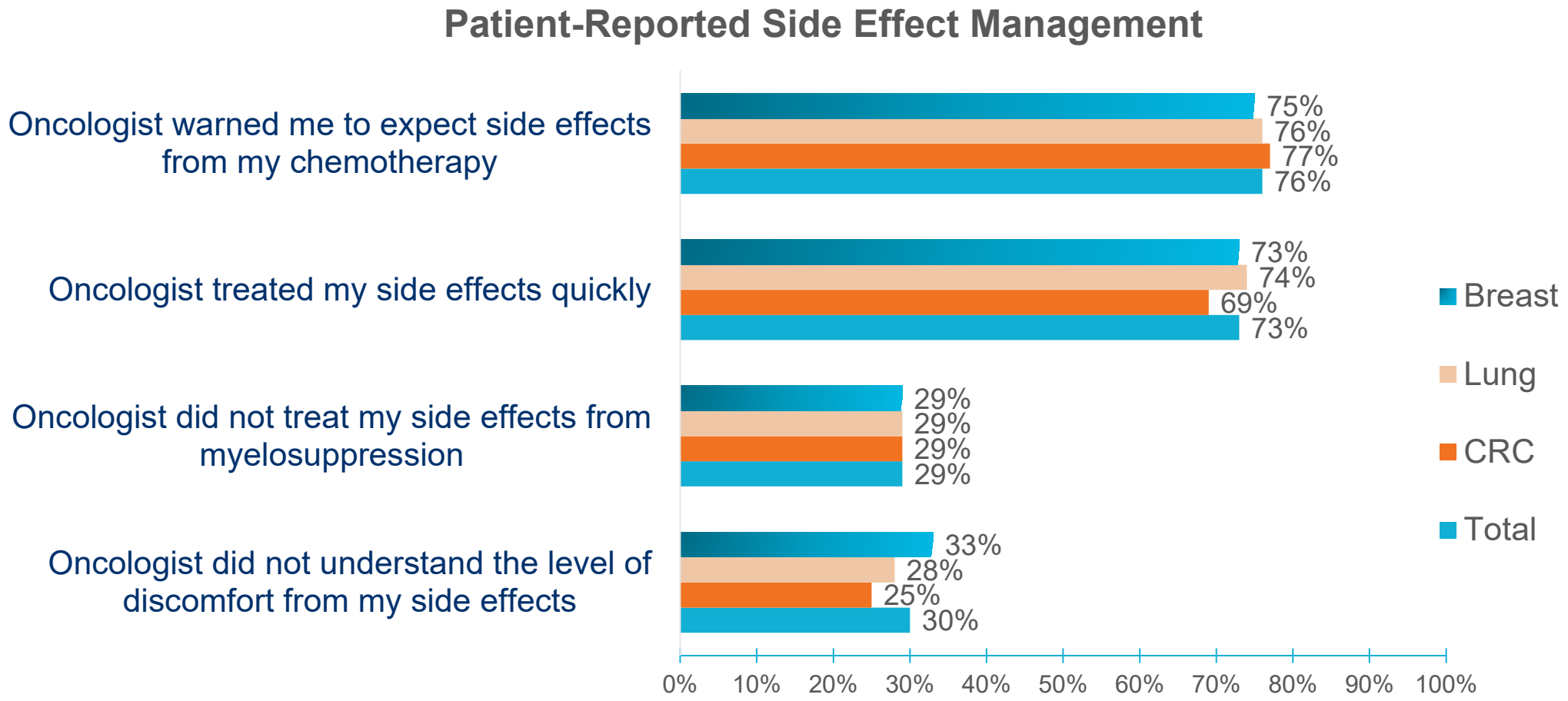


Despite available rescue interventions, chemotherapy dose delays, reductions, discontinuations, or regimen changes were reported by 2/3 of patients

Abbreviations: ESA, erythropoiesis-stimulating agent; G(M)-CSF, granulocyte (macrophage) colony-stimulating factor; RBC, red blood cell.

Epstein RS, et al. *Adv Ther*. 2020; epub online July 8, 2020.

Real-World Management of Chemotherapy-Induced Myelosuppression



Abbreviations: CRC, colorectal cancer; SE, side effect.

Epstein RS, et al. *Adv Ther*. 2020; epub online July 8, 2020.

Real-World Financial Burden of Chemotherapy-Induced Myelosuppression in SCLC

	SCLC (N=339)
Grade 3/4 CIN, %	45
Grade 3/4 CIA, %	41
Grade 3/4 CIT, %	25
RBC transfusion, %	43
Platelet transfusion, %	15
Prophylactic G-CSF, %	6
Treatment with G-CSF, %	43
ESA treatment, %	4

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.

Average Annual Per Patient Costs for Grade 3/4 Hematologic Events	
Neutropenia	$131,047
Anemia	$95,954
Thrombocytopenia	$90,053

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

Epstein RS, et al. In: Proc ASCO; May 29-31, 2020; Chicago, IL. Abstract e19300.

G1 THERAPEUTICS

Investigational therapies focused on the root of the problem

Investigational Therapies

Agent	Class	Affect on HSC Lineage	Phase of Study	Active Trials as of July 2020
Benegrastim (F627)	WBC-GF	Stimulates neutrophils	Phase 3	Trials completed in breast cancer
Eflapegrastim	WBC-GF	Stimulates neutrophils	Phase 1	TC followed by eflapegrastim as 1L in ESBC
Plinabulin	Oral vascular microtubule disrupting agent	Accelerates neutrophil maturation and delays apoptosis	Phase 1 Phase 1/2 Phase 3 Phase 3 Phase 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 Phase 3	• Non-myeloid malignancies in patients receiving chemotherapy • Low-risk MDS
Trilaciclib	Intravenous CDK4/6 inhibitor	Protects neutrophils, erythrocytes, and platelets	Phase 1/2 Phase 2 Phase 1/2 Phase 2	• EP ± trilaciclib as 1L in SCLC[a] • 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.

[a]Trial completed.

The National Institutes of Health's clinical trials website. Available at: https://clinicaltrials.gov/. Accessed 7/1/2020.

G1 THERAPEUTICS

Summary Thoughts

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

G1 THERAPEUTICS

Thank you for your attention

Tell us what you think