CHEMOTHERAPY-INDUCED THROMBOCYTOPENIA (CIT)

Thrombocytopenia in Cancer Patients

Chemotherapy-induced thrombocytopenia (CIT) is a serious, treatment-limiting complication associated with chemotherapy (and other cancer therapies), and is generally defined as platelet counts <100 x 10^9/L[1]

Severity of thrombocytopenia is based on platelet counts and is graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (1–5, from normal to most severe)[2]

Grade	1	2	3	4	5
Platelet count (x 10^9/L)	<LLN–75	<75–50	<50–25	<25	–

LLN = Lower Limit of Normal

Severely low platelet counts can negatively impact treatment outcomes by disrupting therapy,[3] increasing the risk of bleeding[4] and need for platelet transfusions[5]

Patients can develop thrombocytopenia through a variety of disease- or treatment-related mechanisms

Causes of thrombocytopenia in cancer patients

Disease-related[6–8]
- Bone marrow involvement
- Splenomegaly due to tumor enlargement
- Liver involvement

Treatment-related[1,8]
- Cytotoxic chemotherapy
- Targeted therapy
- Radiation

Cytotoxic chemotherapies are the most common cause of treatment-related thrombocytopenia[8]

Epidemiology

CIT is most commonly noted in both solid tumors and hematologic malignancies across multiple therapeutic agents; these rates are dependent upon tumor type and specific cancer therapy[9]

Prevalence of CIT was assessed in a retrospective study of 47,159 patients with solid tumors or hematopoeitic malignancies[9]

Prevalence of CIT according to solid tumor type and specific cancer therapy

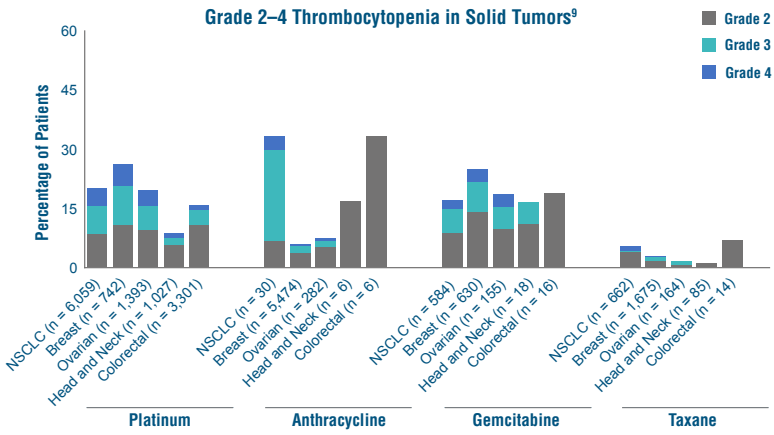
Grade 2–4 CIT Prevalence by Therapy[9,*,†]	
Gemcitabine-based	23.2%
Platinum-based	19.9%
Anthracycline-based	10.1%
Taxane-based	4.3%

Prevalence by Solid Tumor Type[9,*]	
Colorectal	61.7%
Non-small cell lung	50.5%
Ovarian	45.6%
Breast	37.6%

*According to study, is defined as platelet count <150 x 10^9/L
†Includes solid tumors and hematologic malignancies

Grade 3–4 CIT prevalence was highest in non-small cell lung cancer (NSCLC; **10.7**%), lowest in head and neck cancer (2.8%)[9,*]

CIT is a potential complication in many patients with cancer, with rates highly dependent upon tumor type



Reference list: 1. Kuter DJ. *Oncology (Williston Park).* 2015;29:282-294. 2. *US Department of Health and Human Services. Common Terminology Criteria for Adverse Events (CTCAE) Version 4.03.* June 14, 2010. http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_5x7.pdf. Accessed April 18, 2018. 3. Elting LS, et al. *J Clin Oncol.* 2001;19:1137-1146. 4. Cairo MS. *Oncology (Williston Park).* 2000;14:21-31. 5. Kaufman RM, et al. *Ann Intern Med.* 2015;162:205-213. 6. Liebman HA. *Thromb Res.* 2014; 133;Suppl 2:S63-S69. 7. Li VJ, et al. Presented at: American Society of Hematology; December 9–12, 2017; Atlanta, GA. Abstract 2324. 8. Piatek CI, Liebman HA. In: Gresele P, Kleiman NS, Lopez JA, Page CP, eds. *Platelets in Thrombotic and Non-Thrombotic Disorders.* Springer; 2017:841-850. 9. Wu Y, et al. *Clin Ther.* 2009;31(pt 2):2416-2432. 10. Zeuner A, et al. *Cancer Res.* 2007;67:4767-4773. 11. Agarwala SS, Kirkwood JM. *Oncologist.* 2000;5:144-151. 12. Cutts SM, et al. *IUBMB Life.* 2005;57:73-81. 13. Dasari S, Tchounwou PB. *Eur J Pharmacol.* 2014;740:364-378. 14. McManus PM, et al. *Blood.* 1984;64(5):1036-1041. 15. Curtis BR, et al. *Am J Hematol.* 2006;81:193-198. 16. Li W, et al. *J Pharmacol Toxicol Methods.* 2006;54(3):313-319. 17. Giovannetti E. *Mol Pharmacol.* 2005;68:110–118. 18. Wang H, et al. *BMC Cancer.* 2014;14:37. 19. Josefsson EC, et al. *J Exp Med.* 2011;208:2017-2031. 20. Berger G, et al. *Blood.* 1998;92:4446-4452. 21. Italiano J, Hartwig J. In: Kerrigan, SW, ed. *The Non-Thrombotic Role of Platelets in Health and Disease.* InTech; 2015; doi: 10.5772/60678. 22. Deutsch VR, Tomer A. *Br J Haematol.* 2006;134:453-466. 23. Vadhan-Raj S, et al. *Semin Hematol.* 2009;46 (1 suppl 2):S26-S32. 24. Loibl S, et al. *BMC Cancer.* 2011;11:131-131. 25. Nagel CI, et al. *Gynecol Oncol.* 2012;124:221-224. 26. Kistanguri G, McCrae KR. *Hematol Oncol Clin North Am.* 2013;27:495. 27. Bonadonna G, et al. *N Engl J Med.* 1995;332:901-906. 28. Elting LS, et al. *Cancer.* 2003;97:1541-1550. 29. CancerNet, https://www.cancer.net/navigating-cancer-care/side-effects/thrombocytopenia. Accessed April 18, 2018.

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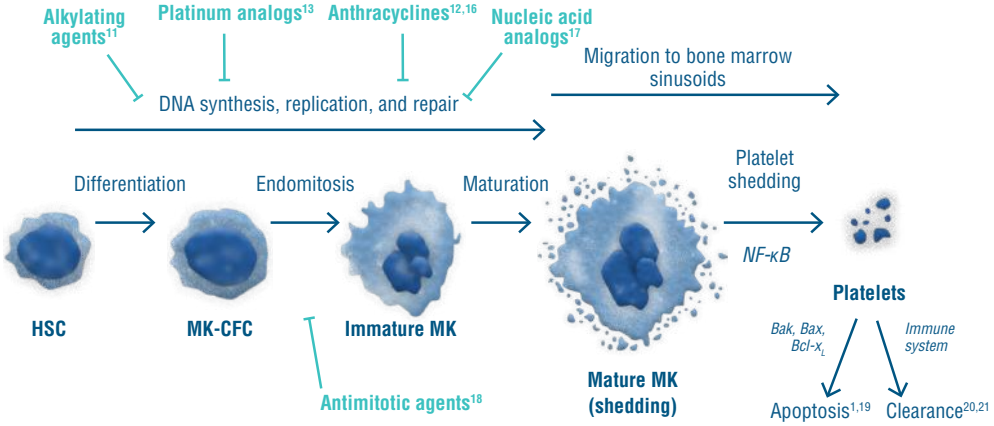
Mechanism of Disease

Chemotherapeutic agents can interrupt platelet production through multiple pathways, including DNA synthesis, DNA repair, platelet shedding, and clearance of platelets. Some chemotherapies may act to increase the rate of platelet destruction[4]

- Alkylating agents, platinum analogs, anthracyclines, and nucleic acid analogs act to inhibit DNA synthesis, replication, or repair at different points in megakaryocyte development, leading to megakaryocyte progenitor cell death[10–14]
- Oxaliplatin-dependent antibodies can cross-react with platelet antigens, leading to a rapid drop in platelet count and bleeding symptoms[15]



Platelets are produced by megakaryocytes (MKs) in the bone marrow and naturally destroyed through multiple mechanisms (apoptosis and clearance in the spleen and liver) in order to maintain homeostasis[21]

Thrombopoietin is the most potent endogenous cytokine for stimulating megakaryocyte proliferation, maturation, and formation of proplatelets, which fragment to platelets[22]

Clinical Burden of Disease

CIT is a major cause of chemotherapy disruption, including dose delays and/or reductions, that may negatively affect treatment outcomes and increase the risk of bleeding events and the need for platelet transfusions

CHEMOTHERAPY DOSE DELAYS AND/OR REDUCTIONS

CIT is often managed by reducing or delaying chemotherapy that could result in suboptimal treatment outcomes, and is often attributed directly to thrombocytopenia[8, 23]

Outcomes of suboptimal treatment are evaluated based on the relative dose intensity[24]

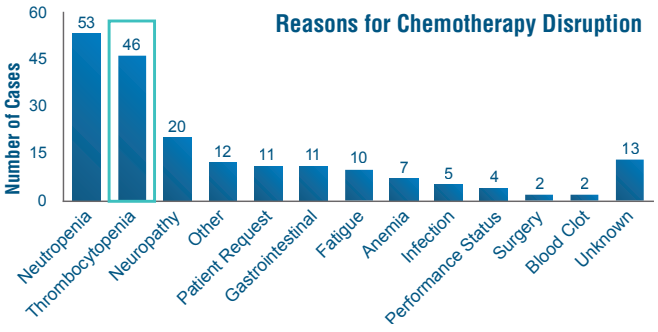
$$\text{Dose intensity} = \frac{\text{Total dose delivered}}{\text{Time to complete therapy}}$$

⇩DOSE / TIME
DOSE / ⇧TIME
→ ⇩DOSE INTENSITY

$$\text{Relative dose intensity (\%)} = \frac{\text{Delivered dose intensity}}{\text{Standard dose intensity*}} \times 100$$

In a retrospective analysis of 158 patients with primary epithelial ovarian, peritoneal, or fallopian tube carcinoma, 83 patients experienced chemotherapy disruption[25]

- Thrombocytopenia was the second-leading cause of dose disruption



Potential complications of CIT include:

- **Chemotherapy dose disruption[3,10]** — Decreased relative dose intensity
- **Bleeding episodes[3,26]** — E.g.: epistaxis, ecchymosis, petechiae, mucosal bleeding, GI bleeding
- **Survival disadvantage[27]**
- **Increased healthcare utilization[28]**

INCREASED RISK OF BLEEDING

Risk of bleeding is inversely related to platelet count, although this may vary between patients and there are no good predictors of bleeding in thrombocytopenic patients[4]

Platelet count	<10 x 10^9/L	10–19 x 10^9/L	20–49 x 10^9/L
Reported bleeding	38% 21 cycles	12% 52 cycles	10% 197 cycles

Major bleeding episodes have been shown to be significantly associated with shorter survival[3]

INCREASED NEED FOR PLATELET TRANSFUSION

Surgical procedures can be delayed or complicated by bleeding at platelet counts <50 x 10^9/L, and prophylactic platelet transfusions may be necessary[1,5]

- Surgery may be delayed until platelet count recovers[29]
- Platelet transfusions are recommended by the American Association of Blood Banks at platelet counts <50 x 10^9/L for major non-neuraxial procedures[5]