BÖLÜM 12

Kanser Hastalarında Granülosit Koloni Uyarıcı Faktör (G-CSF) Kullanımı

Savaş GÖKÇEK [1]

GİRİŞ

Granülositler ve makrofajlar, vücudu bakteriyel, viral ve mantar enfeksiyonlarına karşı koruyan doğal bağışıklık sistemi üyeleridir. Çoğu kısa ömürlüdürler ve kemik iliğinde oluşan yeni hücrelerle sürekli değiştirilirler. Normal şartlar altında bu hücrelerin sayısı oldukça sabittir ve bu da sıkı bir kontrol sayesinde olur. Enfeksiyon durumunda, granülosit ve makrofaj üretimi hızla artırılabilir.

Kemik iliği hücrelerinin bu üretimi, koloni uyarıcı faktörler (CSF) denilen glikoprotein molekülleri tarafından sağlanmıştır. Dolaşımdayken, CSF'ler uygun hedef hücreler üzerinde oldukça spesifik etkilere sahip hormonlara benzeyebilir. Diğer durumlarda, CSF'ler oldukça lokalize bölgelerde üretilebilir ve etki gösterebilirler. Hormonların aksine, CSF'ler tek bir hücre tipinin ürünü değildir ve gerektiğinde vücuttaki hemen hemen her organ veya hücre tipi tarafından üretilebilir (1).

Bazı durumlarda, CSF'ler kendi aralarında veya diğer bazı sitokinlerle sinerjik etkileşime girebilirler. CSF'ler kök hücrelerin ve granülosit ve makrofajların erken öncüllerinin oluşumunun kontrolünde kemik iliğindeki mikroçevresel hücrelerle etkileşime girebilir.

GRANÜLOSİTLERİN VE MAKROFAJLARIN ATALARI

Hematopoetik popülasyonlar hiyerarşik bir şekilde organize edilir (Şekil 1). Sınırlı sayıda, kendini yenileyen multipotansiyel hematopoetik kök hücre, tüm

[1] Uzm. Dr., Dokuz Eylül Üniversite Hastanesi Tıbbi Onkoloji BD., gokceksavas35@gmail.com, ORCID iD:0000-0001-5928-0447

Malignitenin Olası Uyarılması

Miyeloid büyüme faktörü reseptörleri çeşitli hematopoetik ve hematopoetik olmayan hücre tipleri tarafından ifade edildiğinden, bazı malign hücre soylarının granülosit CSF ile tedaviye yanıt verebileceği, potansiyel olarak altta yatan durumu kötüleştirebileceği veya duyarlı bir bireyde malignite gelişimini tetikleyebileceği endişesi olmuştur. Bu tür bir endişeye örnek olarak, akut miyeloid lösemi (AML) için indüksiyon tedavisi gören hastalarda G-CSF'lerin kullanımı, malign miyeloblastların bu tür büyüme faktörleri için reseptörler ifade ettiğine dair kanıtlar nedeniyle sınırlandırılmıştır. AML kemoterapisi sırasında CSFlerden ziyade profilaktik antibakteriyel ve antifungal ajanlar daha yaygın olarak kullanılmaktadır.

Bazı gözlemsel çalışmalar, meme ve akciğer kanseri gibi diğer maligniteler için kemoterapi sırasında CSF kullanımının AML, miyelodisplastik sendrom (MDS) ve muhtemelen akut lenfoblastik lösemi/lenfositik lenfoma (ALL/LL) dahil olmak üzere tedaviye bağlı hematolojik neoplazm riskinde küçük ama muhtemelen gerçek bir artışla ilişkili olduğunu bildirmektedir (59-61) :

Dolayısıyla, kemoterapi sırasında miyeloid büyüme faktörlerinin kullanılması tedaviyle ilişkili hematolojik neoplazm riskini artırsa da, riskin mutlak büyüklüğü küçüktür ve risk muhtemelen bu ortamda CSF kullanımının faydalarından daha ağır basmaktadır. Bununla birlikte, Ocak 2021'de, hem filgrastim hem de pegfilgrastim için Amerika Birleşik Devletleri Reçete Bilgileri, akciğer kanseri için kemoterapi ve/veya radyoterapi sonrası her iki ajanla da hem MDS hem de AML riskini belirtecek ve hastaların bu ortamlarda AML/MDS belirti ve semptomları açısından izlenmesi gerektiğini belirtecek şekilde değiştirilmiştir (62,63) .

KAYNAKLAR

1. Metcalf D. Foundations in Cancer Research. Hemopoietic regulators and leukemia development: A personal retrospective. *Advances in Cancer Research.* 1994;6:41–91. [PubMed] [Google Scholar]
2. Furth J. Conditioned and autonomous neoplasms: A review. *Cancer Res.* 1953;13:477–492. [PubMed] [Google Scholar]
3. Furth J. The concept of conditioned and autonomous neoplasms. *Leuk. Res. Ciba Found. Symp.* 1954:38–41. [Google Scholar]
4. Bradley TR, Metcalf D. The growth of mouse bone marrow cells *in vitro*. *Australian Journal of Experimental Biology and Medical Science.* 1966;44:287–300. [PubMed] [Google Scholar]
5. Ichikawa Y, Pluznik DH, Sachs L. *In vitro* control of the development of macrophage and granulocyte colonies. *Proceedings of the National Academy of Sciences, USA*. 1966;56:488–495. [PMC free article] [PubMed] [Google Scholar]

6. Pluznik DH, Sachs L. The induction of clones of normal"mast" cells by a substance in conditioned medium. *Experimental Cell Research.* 1966;43:553–563. [PubMed] [Google Scholar]
7. Robinson WA, Metcalf D, Bradley TR. Stimulation by normal and leukaemic mouse sera of colony formation *in vitro* by mouse bone marrow cells. *Journal of Cellular and Comparative Physiology.* 1967;69:83–92. [Google Scholar]
8. Pike BL, Robinson WA. Human bone marrow colony growth in agar-gel. *J. Cell Physiol.* 1970;76:77–84. [PubMed] [Google Scholar]
9. Stanley ER, Metcalf D. Partial purification of some properties of the factor in normal and leukaemic human urine stimulating mouse bone marrow colony growth *in vitro*. *Australian Journal of Experimental Biology and Medical Science.* 1969;47:467–483. [PubMed] [Google Scholar]
10. Burgess AW, Camakaris J, Metcalf D. Purification and properties of colony-stimulating factor from mouse lung conditioned medium. *Journal of Biological Chemistry.* 1977;252:1998–2003. [PubMed] [Google Scholar]
11. Stanley ER, Heard PM. Factors regulating macrophage production and growth: Purification and some properties of the colony stimulating factor from medium conditioned by mouse L cells. *Journal of Biological Chemistry.* 1977;252:4305–4312. [PubMed] [Google Scholar]
12. Ihle JN, Keller J, Henderson L, Klein F, Palaszynski E. Procedures for the purification of interleukin 3 to homogeneity. *Journal of Immunology.* 1982;129:2431–2436. [PubMed] [Google Scholar]
13. Nicola NA, Metcalf D, Matsumoto M, Johnson GR. Purification of a factor inducing differentiation in murine myelomonocytic leukemia cells: Identification as granulocyte colony-stimulating factor. *Journal of Biological Chemistry.* 1983;258:9017–9023. [PubMed] [Google Scholar]
14. Gasson JC, et al. Purified human granulocyte-macrophage colony-stimulating factor: Direct action on neutrophils. *Science (Washington)* 1984;266:1339–1342. [PubMed] [Google Scholar]
15. Welte KE, et al. Purification and biochemical characterization of human pluripotent hematopoietic colony-stimulating factor. *Proceedings of the National Academy of Sciences, USA.* 1985;82:1526–1530. [PMC free article] [PubMed] [Google Scholar]
16. Wong GG, et al. Human GM-CSF: Molecular cloning of the complementary DNA and purification of the natural and recombinant proteins. *Science (Washington)* 1985;228:810–815. [PubMed] [Google Scholar]
17. Nomura H, et al. Purification and characterization of human granulocyte colony-stimulating factor (G-CSF) *EMBO Journal.* 1986;5:871–876. [PMC free article] [PubMed] [Google Scholar]
18. Zenke G, et al. Purification and characterization of natural human interleukin-3. *Lymphokine and Cytokine Research.* 1991;10:329–335. [PubMed] [Google Scholar]
19. Caggiano V, Weiss RV, Rickert TS, Linde-Zwirble WT. Incidence, cost, and mortality of neutropenia hospitalization associated with chemotherapy. Cancer 2005; 103:1916.
20. Freifeld AG, Bow EJ, Sepkowitz KA, et al. Clinical practice guideline for the use of antimicrobial agents in neutropenic patients with cancer: 2010 update by the infectious diseases society of america. Clin Infect Dis 2011; 52:e56.
21. Smith TJ, Bohlke K, Lyman GH, et al. Recommendations for the Use of WBC Growth Factors: American Society of Clinical Oncology Clinical Practice Guideline Update. J Clin Oncol 2015; 33:3199.
22. National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology. Head and neck cancer. Version 1.2021. Available at: https://www.nccn.org/professionals/physician_gls/ https://www.nccn.org/professionals/physician_gls/ (Accessed on January 29, 2020).

23. Klastersky J, de Naurois J, Rolston K, et al. Management of febrile neutropaenia: ESMO Clinical Practice Guidelines. Ann Oncol 2016; 27:v111.
24. National Comprehensive Cancer Network (NCCN). NCCN clinical practice guidelines in oncology. Available at: https://www.nccn.org/professionals/physician_gls (Accessed on May 18, 2022).
25. Ozer H, Armitage JO, Bennett CL, et al. 2000 update of recommendations for the use of hematopoietic colony-stimulating factors: evidence-based, clinical practice guidelines. American Society of Clinical Oncology Growth Factors Expert Panel. J Clin Oncol 2000; 18:3558.
26. Kuderer NM, Dale DC, Crawford J, Lyman GH. Impact of primary prophylaxis with granulocyte colony-stimulating factor on febrile neutropenia and mortality in adult cancer patients receiving chemotherapy: a systematic review. J Clin Oncol 2007; 25:3158.
27. Sung L, Nathan PC, Alibhai SM, et al. Meta-analysis: effect of prophylactic hematopoietic colony-stimulating factors on mortality and outcomes of infection. Ann Intern Med 2007; 147:400.
28. Cooper KL, Madan J, Whyte S, et al. Granulocyte colony-stimulating factors for febrile neutropenia prophylaxis following chemotherapy: systematic review and meta-analysis. BMC Cancer 2011; 11:404.
29. Wang L, Baser O, Kutikova L, et al. The impact of primary prophylaxis with granulocyte colony-stimulating factors on febrile neutropenia during chemotherapy: a systematic review and meta-analysis of randomized controlled trials. Support Care Cancer 2015; 23:3131.
30. Weycker D, Li X, Barron R, et al. Importance of Risk Factors for Febrile Neutropenia Among Patients Receiving Chemotherapy Regimens Not Classified as High-Risk in Guidelines for Myeloid Growth Factor Use. J Natl Compr Canc Netw 2015; 13:979.
31. Aapro M, Schwenkglenks M, Lyman GH, et al. Pegfilgrastim primary prophylaxis vs. current practice neutropenia management in elderly breast cancer patients receiving chemotherapy. Crit Rev Oncol Hematol 2010; 74:203.
32. Tjan-Heijnen VC, Postmus PE, Ardizzoni A, et al. Reduction of chemotherapy-induced febrile leucopenia by prophylactic use of ciprofloxacin and roxithromycin in small-cell lung cancer patients: an EORTC double-blind placebo-controlled phase III study. Ann Oncol 2001; 12:1359.
33. Dranitsaris G, Rayson D, Vincent M, et al. Identifying patients at high risk for neutropenic complications during chemotherapy for metastatic breast cancer with doxorubicin or pegylated liposomal doxorubicin: the development of a prediction model. Am J Clin Oncol 2008; 31:369.
34 Lyman GH, Kuderer NM, Crawford J, et al. Predicting individual risk of neutropenic complications in patients receiving cancer chemotherapy. Cancer 2011; 117:1917.
35. Moreau M, Klastersky J, Schwarzbold A, et al. A general chemotherapy myelotoxicity score to predict febrile neutropenia in hematological malignancies. Ann Oncol 2009; 20:513.
36. Sharma S, Rezai K, Driscoll D, et al. Characterization of neutropenic fever in patients receiving first-line adjuvant chemotherapy for epithelial ovarian cancer. Gynecol Oncol 2006; 103:181.
37. Herskovic A, Martz K, al-Sarraf M, et al. Combined chemotherapy and radiotherapy compared with radiotherapy alone in patients with cancer of the esophagus. N Engl J Med 1992; 326:1593.
38. Pignon JP, Arriagada R, Ihde DC, et al. A meta-analysis of thoracic radiotherapy for small-cell lung cancer. N Engl J Med 1992; 327:1618.
39. Bunn PA Jr, Crowley J, Kelly K, et al. Chemoradiotherapy with or without granulocyte-macrophage colony-stimulating factor in the treatment of limited-stage small-cell lung cancer: a prospective phase III randomized study of the Southwest Oncology Group. J Clin Oncol 1995; 13:1632.

40. Staar S, Rudat V, Stuetzer H, et al. Intensified hyperfractionated accelerated radiotherapy limits the additional benefit of simultaneous chemotherapy--results of a multicentric randomized German trial in advanced head-and-neck cancer. Int J Radiat Oncol Biol Phys 2001; 50:1161.
41. Haim N, Shulman K, Goldberg H, Tsalic M. The safety of full-dose chemotherapy with secondary prophylactic granulocyte colony stimulating factor (G-CSF) following a prior cycle with febrile neutropenia. Med Oncol 2005; 22:229.
42. Chouaid C, Bassinet L, Fuhrman C, et al. Routine use of granulocyte colony-stimulating factor is not cost-effective and does not increase patient comfort in the treatment of small-cell lung cancer: an analysis using a Markov model. J Clin Oncol 1998; 16:2700.
43. Crawford J, Ozer H, Stoller R, et al. Reduction by granulocyte colony-stimulating factor of fever and neutropenia induced by chemotherapy in patients with small-cell lung cancer. N Engl J Med 1991; 325:164.
44. Debled M, Houédé N, Madranges N, et al. Does chemotherapy-induced neutropaenia result in a postponement of adjuvant or neoadjuvant regimens in breast cancer patients? Results of a retrospective analysis. Br J Cancer 2007; 97:1642.
45. Hartmann LC, Tschetter LK, Habermann TM, et al. Granulocyte colony-stimulating factor in severe chemotherapy-induced afebrile neutropenia. N Engl J Med 1997; 336:1776.
46. Mhaskar R, Clark OA, Lyman G, et al. Colony-stimulating factors for chemotherapy-induced febrile neutropenia. Cochrane Database Syst Rev 2014; :CD003039.
47. Kuderer NM, Dale DC, Crawford J, et al. Mortality, morbidity, and cost associated with febrile neutropenia in adult cancer patients. Cancer 2006; 106:2258.
48. NCCN guidelines for supportive care available online at https://www.nccn.org/professionals/physician_gls/#supportive (Accessed on June 16, 2020).
49. Clemons M, Fergusson D, Simos D, et al. A multicentre, randomised trial comparing schedules of G-CSF (filgrastim) administration for primary prophylaxis of chemotherapy-induced febrile neutropenia in early stage breast cancer. Ann Oncol 2020; 31:951.
50. Skarlos DV, Timotheadou E, Galani E, et al. Pegfilgrastim administered on the same day with dose-dense adjuvant chemotherapy for breast cancer is associated with a higher incidence of febrile neutropenia as compared to conventional growth factor support: matched case-control study of the Hellenic Cooperative Oncology Group. Oncology 2009; 77:107.
51. Spunt SL, Irving H, Frost J, et al. Phase II, randomized, open-label study of pegfilgrastim-supported VDC/IE chemotherapy in pediatric sarcoma patients. J Clin Oncol 2010; 28:1329.
52. Lyman GH, Allcott K, Garcia J, et al. The effectiveness and safety of same-day versus next-day administration of long-acting granulocyte colony-stimulating factors for the prophylaxis of chemotherapy-induced neutropenia: a systematic review. Support Care Cancer 2017; 25:2619.
53. Green MD, Koelbl H, Baselga J, et al. A randomized double-blind multicenter phase III study of fixed-dose single-administration pegfilgrastim versus daily filgrastim in patients receiving myelosuppressive chemotherapy. Ann Oncol 2003; 14:29.
54. Holmes FA, O'Shaughnessy JA, Vukelja S, et al. Blinded, randomized, multicenter study to evaluate single administration pegfilgrastim once per cycle versus daily filgrastim as an adjunct to chemotherapy in patients with high-risk stage II or stage III/IV breast cancer. J Clin Oncol 2002; 20:727.
55. Haim N, Shulman K, Goldberg H, Tsalic M. The safety of full-dose chemotherapy with secondary prophylactic granulocyte colony stimulating factor (G-CSF) following a prior cycle with febrile neutropenia. Med Oncol 2005; 22:229.
56. Fox E, Widemann BC, Hawkins DS, et al. Randomized trial and pharmacokinetic study of pegfilgrastim versus filgrastim after dose-intensive chemotherapy in young adults and children with sarcomas. Clin Cancer Res 2009; 15:7361.

57. Shi YK, Chen Q, Zhu YZ, et al. Pegylated filgrastim is comparable with filgrastim as support for commonly used chemotherapy regimens: a multicenter, randomized, crossover phase 3 study. Anticancer Drugs 2013; 24:641.
58. Pfeil AM, Allcott K, Pettengell R, et al. Efficacy, effectiveness and safety of long-acting granulocyte colony-stimulating factors for prophylaxis of chemotherapy-induced neutropenia in patients with cancer: a systematic review. Support Care Cancer 2015; 23:525.
59. Lyman GH, Yau L, Nakov R, Krendyukov A. Overall survival and risk of second malignancies with cancer chemotherapy and G-CSF support. Ann Oncol 2018; 29:1903.
60. Jabagi MJ, Vey N, Goncalves A, et al. Risk of secondary hematologic malignancies associated with breast cancer chemotherapy and G-CSF support: A nationwide population-based cohort. Int J Cancer 2021; 148:375.
61. Jabagi MJ, Goncalves A, Vey N, et al. Risk of Hematologic Malignant Neoplasms after Postoperative Treatment of Breast Cancer. Cancers (Basel) 2019; 11.
62. https://www.accessdata.fda.gov/drugsatfda_docs/appletter/2021/103353orig1s5196ltr.pdf (Accessed on January 12, 2021). Beveridge RA, Miller JA, Kales AN, et al. A comparison of efficacy of sargramostim (yeast-derived RhuGM-CSF) and filgrastim (bacteria-derived RhuG-CSF) in the therapeutic setting of chemotherapy-induced myelosuppression. Cancer Invest 1998; 16:366.
63. https://www.accessdata.fda.gov/drugsatfda_docs/appletter/2021/125031Orig1s202ltr.pdf (Accessed on January 12, 2021).