BÖLÜM 24

L-ASPARAGİNAZ, OMACETAXİNE, HİDROKSİÜRE VE ENHANCER OF ZESTE HOMOLOG 2 (EZH-2) İNHİBİTÖRLERİ

Narin Yıldırım DOĞAN[1]
Ali DOĞAN[2]

L-ASPARAGİNAZ

Escherichia coli (E. coli) kökenli bir polipeptit olan L-asparaginaz (LA), Akut lenfoblastik lösemi (ALL) tedavi protokolünün önemli bir ilacıdır. LA'nın 1953' de lenfomalarda büyümeyi engellediği saptandı ve 1961'li yıllarda ALL tedavisinde antilösemik olarak kullanılmaya başlandı (1,2). Özellikle çocukluk döneminde ve 40 yaş altı erişkinlerde ALL tedavisinde; vinkristin ve metilprednizolon/deksametazon ile beraber kemoterapi protokolünün önemli bir bileşenidir. ALL tedavisinde uzun yıllardır kullanılan bu ilaç başarıyı önemli derecede arttırmıştır.

Etki Mekanizması

Aminohidrolaz olarak biline LA (L-asparagine amidohydrolase, EC 3.5.1.1); lösemik hücreler için esansiyel bir aminoasit olan L-asparajini, amonyak ve aspartik aside dönüştürür (3). Böylece LA kanda serbest dolaşan L-asparajini tüketir. Normal hücrelerde asparajin sentetaz enzimi olduğu için aspartik asit ve glutaminden L-asparajin sentezi yapılır. Fakat lösemik hücrelerde asparajin sentetaz enzimi eksik olduğundan L-asparajin sentezi yapılamadığından lösemi hücresi için gerekli olan esansiyel aminoasit üretilemez (1,3). LA, Lenfoblastlarda protein biyosentezini inhibe eder. Ayrıca LA albümin, koagülasyon faktörleri, tiroksin bağlayan globülin gibi hepatik protein sentezini inhibe ederek lösemi hücresinin beslenmesini ve çoğalmasını engeller (1,3).

[1] Uzm. Dr., SBÜ Van Eğitim ve Araştırma Hastanesi, İç Hastalıkları Bölümü, narindogan44@gmail.com
[2] Doç. Dr., Van Yüzüncü Yıl Üniversitesi, Tıp Fakültesi, Hematoloji BD., dr.alidogan44@gmail.com

KAYNAKLAR

1. Saadet Akarsu, Erdal Yılmaz, A. Denizmen Aygün, Sevgi Gözdaşoğlu4. Akut lenfoblastik lösemili çocuklarda L-asparajinaz tedavisi ve komplikasyonları. *Türk Pediatri Arşivi.* 2004; 39: 162- 170.
2. Ali Bay, Ahmet Faik Öner, Yaşar Cesur, Cengiz Demir, Yurdagül Mukul, Mehmet Açıkgöz. Çocukluk Çağı Akut Lenfoblastik Lösemi Olgularında L-Asparajinaz'a Bağlı Toksisite. *Van Tıp Dergisi*. 2005; 12 (2):149-152.
3. Tahira Batool & Essam A. Makky & Muna Jalal & Mashitah M. Yusoff. A Comprehensive Review on L-Asparaginase and Its Applications. *Appl Biochem Biotechnol*. 2016; 178:900–923.
4. Verma, N., Bansal, M., & Kumar, S. (2012).Whole cell based miniaturized fiber optic biosensor to monitör L-asparagine. Journal of *Applied Sciences Research*, 3, 809–814.
5. Subhash Chand, Richi V. Mahajan, Jai Prakash Prasad, Debendra K. Sahoo, Kanti Nandan Mihooliya, Mahesh S. Dhar, Girish Sharma. A comprehensive review on microbial L-asparaginase: Bioprocessing, characterization, and industrial applications. *International Union of Biochemistry and Molecular Biology*. 2020; p: 1–29.
6. Angiolillo AL, Schore RJ, Devidas M, et al. Pharmacokinetic and pharmacodynamic properties of calaspargase pegol Escherichia coli L-asparaginase in the treatment of patients with acute lymphoblastic leukemia: results from Children's Oncology Group Study AALL07P4. *J Clin Oncol* 2014; 32:3874.
7. Otten J, Philippe N, Suciu S, et al. The children leukemias group, 30 years of research and achievements. *Eur J Cancer*. 2002; 38: 44- 49.
8. Silverman LB, Levy DE, Dalton VK, et al. Erwinia L-asparaginase is less toxic and less effective than E. coli L-asparaginase in Proc Am Soc *Clin Oncol* 2002; 21: 389.
9. Dinndorf PA, Gootenberg J, Cohen MH, et al. FDA drug approval summary: pegaspargase (oncaspar) for the first-line treatment of children with acute lymphoblastic leukemia. *Oncologist* 2007; 12:991.
10. HemOnc.org - A Hematology Oncology Wiki 2022. (05/10/2022 tarihinde (https://hemonc.org/wiki/B-cell acute lymphoblastic leukemia adresinden ulaşılmıştır).
11. Salzer,W. L., Asselin, B. L., Plourde, P. V., Corn, T., & Hunger, S. P.Development of asparaginase Erwinia chrysanthemi for the treatment of acute lymphoblastic leukemia. *Annals of the New York Academy of Sciences,* 2014; 1329: 81–92.
12. Vrooman LM et al. Activity and toxicity of intravenous Erwinia asparaginase following allergy to E. Coli-derived asparaginase in children and adolescents with acute lymphoblastic leukemia. *Pediatr Blood Cancer 2016;* 63(2):228–233.
13. Lenz HJ. Management and preparedness for infusion and hypersensitivity reactions. *Oncologist* 2007; 12:601.
14. Petersen WC Jr, Clark D, Senn SL, et al. Comparison of allergic reactions to intravenous and intramuscular pegaspargase in children with acute lymphoblastic leukemia. *Pediatr Hematol Oncol* 2014; 31:311.
15. Liu Y, Smith CA, Panetta JC, et al. Antibodies Predict Pegaspargase Allergic Reactions and Failure of Rechallenge. *J Clin Oncol* 2019; 37:2051.
16. Cooper SL, Young DJ, Bowen CJ, et al. Universal premedication and therapeutic drug monitoring for asparaginase-based therapy prevents infusion-associated acute adverse events and drug substitutions. *Pediatr Blood Cancer* 2019; 66:e27797.
17. Gurel G, Blaha G, Moore PB, Steitz TA. U2504 determines the species specificity of the A-site cleft antibiotics: the structures of tiamulin, homoharringtonine, and bruceantin bound to the ribosome. *J Mol Biol.* 2009; 389:146–56.
18. Varsha Gandhi, William Plunkett, and Jorge E. Cortes. Omacetaxine: a protein translation inhibitor for treatment of chronic myelogenous leukemias. *Clin Cancer Res.* 2014; 20(7): 1735–1740.
19. Cortes J, Lipton JH, Rea D, et al. Phase 2 study of subcutaneous omacetaxine mepesuccinate after TKI failure in patients with chronic-phase CML with T315I mutation. *Blood* 2012; 120:2573.
20. Cortes J, Digumarti R, Parikh PM, et al. Phase 2 study of subcutaneous omacetaxine mepesuccinate for chronic-phase chronic myeloid leukemia patients resistant to or intolerant of tyrosine kinase inhibitors. *Am J Hematol* 2013; 88:350.

21. Cortes JE, Kantarjian HM, Rea D, et al. Final analysis of the efficacy and safety of omacetaxine mepesuccinate in patients with chronic- or accelerated-phase chronic myeloid leukemia: Results with 24 months of follow-up. *Cancer* 2015; 121:1637.
22. Wellstein A, Giaccone G, Atkins MB, Sausville EA. Hydroxyurea. Cytotoxic drugs. In, Brunton LL, Hilal-Dandan R, Knollman BC, eds. Goodman & Gilman's the pharmacological basis of therapeutics. 13th ed. New York: *McGraw-Hill,* 2018, pp. 1195-1196.
23. Brawley OW, Cornelius LJ, Edwards LR, et al. National Institutes of Health Consensus Development Conference Statement: Hydroxyurea Treatment for Sickle Cell Disease. *Ann Intern Med.* 2008;148(12):932-938.
24. Döhner H, Estey EH, Amadori S, et al. Diagnosis and management of acute myeloid leukemia in adults: recommendations from an international expert panel, on behalf of the European LeukemiaNet. *Blood.* 2010;115(3):453-474.
25. Barbui T, Tefferi A, Vannucchi AM, et al. Philadelphia chromosome-negative classical myeloproliferative neoplasms: revised management recommendations from European LeukemiaNet. *Leukemia*. 2018;32(5):1057-1069.
26. Rodgers GP, Dover GJ, Uyesaka N, et al. Augmentation by Erythropoietin of the Fetal-Hemoglobin Response to Hydroxyurea in Sickle Cell Disease. *N Engl J Med*. 1993;328(2):73-80.
27. Ferster A, Tahriri P, Vermylen C, et al. Five Years of Experience With Hydroxyurea in Children and Young Adults With Sickle Cell Disease. *Blood.* 2001;97(11):3628-3632.
28. Antonioli E, Guglielmelli P, Pieri L, et al. Hydroxyurea-related toxicity in 3,411 patients with Ph'-negative MPN. *Am J Hematol.* 2012;87(5):552-554.
29. Worley B, Glassman SJ. Acral keratoses and leucocytoclastic vasculitis occurring during treatment of essential thrombocythaemia with hydroxyurea. *Clin Exp Dermatol.* 2016;41(2):166-169.
30. Mattessich S, Ferenczi K, Lu J. Successful treatment of hydroxyurea-associated panniculitis and vasculitis with low-dose methotrexate. *JAAD* Case Rep. 2017;3(5):422-424.
31. Rose PG, Ali S, Watkins E, et al. Long-Term Follow-Up of a Randomized Trial Comparing Concurrent Single Agent Cisplatin, Cisplatin-Based Combination Chemotherapy, or Hydroxyurea During Pelvic Irradiation for Locally Advanced Cervical Cancer: A Gynecologic Oncology Group Study. *J Clin Oncol.* 2007;25(19):2804-2810.
32. Bilbao-Meseguer I, Rodríguez-Gascón A, Barrasa H, Isla A, Solinís MÁ. Augmented renal clearance in critically ill patients: a systematic review. *Clin Pharmacokinet.* 2018;57(9):1107-1121.
33. Sahoo LK, Kullu BK, Patel S, et al. Study of seminal fluid parameters and fertility of male sickle cell disease patients and potential impact of hydroxyurea treatment. *J Assoc Physicians India*. 2017;65(6):22-25.
34. Baccarani M, Deininger MW, Rosti G, et al. European LeukemiaNet recommendations for the management of chronic myeloid leukemia: 2013. *Blood.* 2013;122(6):872-884.
35. Joseph L, Jean C, Manceau S, et al. Effect of hydroxyurea exposure before puberty on sperm parameters in males with sickle cell disease. *Blood.* 2021;137(6):826-829.
36. Berman E, Druker BJ, Burwick R. Chronic myelogenous leukemia: pregnancy in the era of stopping tyrosine kinase inhibitor therapy. *J Clin Oncol.* 2018;36(12):1250-1256.
37. Montironi R, Cupaiolo R, Kadji C, et al. Management of sickle cell disease during pregnancy: experience in a third-level hospital and future recommendations. *J Matern Fetal Neonatal Med.* 2020:1-9.
38. Ware RE, Marahatta A, Ware JL, McElhinney K, Dong M, Vinks AA. Hydroxyurea exposure in lactation: a pharmacokinetics study (HELPS). *J Pediatr.* 2020;222:236-239.
39. Ran Duan, Wenfang Du and Weijian Guo. EZH2: a novel target for cancer treatment. *Journal of hematology and oncology* 2020. 28;13(1):104.
40. Jennifer K. Lue, Jennifer E. Amengual. Emerging EZH2 Inhibitors and Their Application in Lymphoma. *Current Hematologic Malignancy Reports.* 2018;13:369–382.
41. Edith Julia, Gilles Salles. EZH2 inhibition by tazemetostat: mechanisms of action, safety and efficacy in relapsed/refractory follicular lymphoma. *Future Oncol.* 2021;17(17):2127-2140.
42. Sheridan M Hoy. Tazemetostat: *First Approval. Drugs* 2020. 80(5):513-521.