

BÖLÜM 13

PLATİN ANALOGLARININ KLİNİK KULLANIMLARI VE YAN ETKİ YÖNETİMLERİ

Buğra ÖZTOSUN¹

GİRİŞ

Platin analogları günlük onkoloji pratiğinde yaygın şekilde kullanılmaktadır. Sisplatin, Karboplatin ve Okzaliplatin olmak üzere üç tip platin analogu bulunmaktadır. DNA zincirinde kırıklar oluşturarak etki gösteren bu antineoplastik ilaçlar, tek başlarına, farklı antineoplastiklerle kombine ve radyoterapi ile eş zamanlı radyoduyarlaştırıcı olarak kullanılmaktadırlar(1). Aşağıda bir çok farklı kanser tipinde etkin şekilde kullanılmakta olan bu antineoplastik ajanların klinik kullanımları ve kombinasyon olarak yer aldıkları kemoterapi protokolleri ve yan etki profilleri özetlenmiştir.

SISPLATİN

Sisplatin birinci nesil platin analogudur. Onkoloji pratiğinde geniş kullanım alanı bulunmaktadır. Bu kullanım alanları tablo 1. de özetlenmiştir(2).

Adrenokortikal karsinom	Doksorubisin, Etoposid, Mitotan ile
Anal karsinom	Mitomisin ile
Baş Boyun karsinomları	Dosetaksel, 5-Fluorourasil ile kombine veya 5-Fluorourasil ve Setuksimab ile kombine
Endometrium karsinomu	Doksorubisin veya Paklitaksel ile kombine
Gestasyonel trofoblastik neoplazi	EMA-EP protokolü, Etoposid, Metotrekstat, Lökovorin, Daktinomisin ile kombine

¹ Uzm. Dr., İstanbul Medeniyet Üniversitesi, Tıbbi Onkoloji BD., drbugraoztosun@gmail.com

stimülasyonu gibi fiziksel modaliteler veya girişimsel prosedürler endike olabilmektedir(39).

Gastrointestinal yan etkiler içinde bulantı – kusma yaklaşık 60% oranında diğer platin analoglarına benzer sıklıkta görülmekteyken, okzalipatine bağlı diare 46% oranında bildirilmiştir ve diğer platin analoglarından daha sık görülmektedir. Küratif tedavilerde gelişen Grad III ve IV yan etkilerde okzalipatin dozunun 75mg/m²'ye azaltılması, palyatif tedavi süreçlerinde saptanan Grad III – IV yan etkilerde ise dozun 65mg/m²'ye azaltılması önerilmektedir(40).

Kemik iliği supresyonu karboplatin'e göre daha nadir görülmekle birlikte doz kısıtlayıcı olabilen yan etkilerdir. Anemi 64%, Lökopeni 13%, Trombositopeni 30% oranında görülmektedir. Grad IV ve tekrarlayan Grad III hematolojik yan etkilerde hematolojik değerler düzeleneye kadar tedaviye ara verilmesi, sitopeni geriledikten sonra küratif tedavilerde okzalipatin dozunun 75mg/m²'ye, palyatif tedavilerde okzalipatin dozunun 65mg/m²'ye azaltılması önerilmektedir(40).

Okzalipatin tedavisi altında karaciğer metastazına ve diğer hepatit nedenlerine bağlı olmadığı saptanan transaminaz artışı ve portal hipertansiyon gelişimi tespit edildiği takdirde okzalipatine bağlı sinüzoidal obstrüksiyon sendromu düşünülmelidir(41). Sinüzoidal obstrüksiyon sendromu dışında da transaminaz yüksekliği görülebilmektedir, genellikle doz kısıtlayıcı olmamaktadır.

KAYNAKLAR

1. Chu E, T. DeVita V. Physicians Cancer Chemotherapy Drug Manual.; 2022.
2. UpToDate Cisplatin: Drug Information. Published 2022. Accessed October 11, 2022. https://www.uptodate.com/contents/cisplatin-drug-information?search=cisplatin&source=panel_search_result&selectedTitle=1~148&usage_type=panel&kp_tab=drug_general&display_rank=1
3. Krens SD, Lassche G, Jansman FGA, et al. Dose recommendations for anticancer drugs in patients with renal or hepatic impairment. *Lancet Oncol.* 2019;20(4):e200-e207. doi:10.1016/S1470-2045(19)30145-7
4. Plimack ER, Hoffman-Censits JH, Viterbo R, et al. Accelerated methotrexate, vinblastine, doxorubicin, and cisplatin is safe, effective, and efficient neoadjuvant treatment for muscle-invasive bladder cancer: results of a multicenter phase II study with molecular correlates of response and toxicity. *J Clin Oncol.* 2014;32(18):1895-1901. doi:10.1200/JCO.2013.53.2465
5. Galsky MD, Hahn NM, Rosenberg J, et al. A consensus definition of patients with metastatic urothelial carcinoma who are unfit for cisplatin-based chemotherapy. *Lancet Oncol.* 2011;12(3):211-214. doi:10.1016/S1470-2045(10)70275-8
6. Navari RM, Qin R, Ruddy KJ, et al. Olanzapine for the Prevention of Chemotherapy-Induced Nausea and Vomiting. *N Engl J Med.* 2016;375(2):134-142. doi:10.1056/nejmoa1515725
7. Berger MJ, Anand S, Barbour S, et al. NCCN Guidelines Version 2.2022 Antiemesis Continue. Published online 2022. Accessed October 9, 2022. <https://www.nccn.org>
8. Navari RM, Gray SE, Kerr AC. Olanzapine Versus Aprepitant for the Prevention of Chemotherapy-Induced Nausea and Vomiting: A Randomized Phase III Trial. *J Support Oncol.* 2011;9(5):188-195. doi:10.1016/j.suponc.2011.05.002
9. Nakashima K, Murakami H, Yokoyama K, et al. A Phase II study of palonosetron, aprepitant,

- dexamethasone and olanzapine for the prevention of cisplatin-based chemotherapy-induced nausea and vomiting in patients with thoracic malignancy. *Jpn J Clin Oncol.* 2017;47(9):840-843. doi:10.1093/jcco/hyx084
10. Reece PA, Stafford I, Russell J, Khan M, Gill PG. Creatinine clearance as a predictor of ultrafilterable platinum disposition in cancer patients treated with cisplatin: relationship between peak ultrafilterable platinum plasma levels and nephrotoxicity. *J Clin Oncol.* 1987;5(2):304-309. doi:10.1200/JCO.1987.5.2.304
 11. Motwani SS, McMahon GM, Humphreys BD, Partridge AH, Waikar SS, Curhan GC. Development and Validation of a Risk Prediction Model for Acute Kidney Injury After the First Course of Cisplatin. *J Clin Oncol.* 2018;36(7):682-688. doi:10.1200/JCO.2017.75.7161
 12. Suzuki Y, Kanazawa K, Kanai R, et al. A case of primary lung squamous cell carcinoma mimicking malignant mesothelioma producing granulocyte colony stimulating factor with chemotherapy (cisplatin and gemcitabine)-associated thrombotic thrombocytopenic purpura (TTP); An autopsy case report. *Lung Cancer.* 2019;136:105-108. doi:10.1016/J.LUNGCAN.2019.08.018
 13. Perazella MA, Moeckel GW. Nephrotoxicity from chemotherapeutic agents: clinical manifestations, pathobiology, and prevention/therapy. *Semin Nephrol.* 2010;30(6):570-581. doi:10.1016/J.SEMNEPHROL.2010.09.005
 14. Crona DJ, Faso A, Nishijima TE, McGraw KA, Galsky MD, Milowsky MI. A Systematic Review of Strategies to Prevent Cisplatin-Induced Nephrotoxicity. *Oncologist.* 2017;22(5):609-619. doi:10.1634/THEONCOLOGIST.2016-0319
 15. Jordan B, Margulies A, Cardoso F, et al. Systemic anticancer therapy-induced peripheral and central neurotoxicity: ESMO-EONS-EANO Clinical Practice Guidelines for diagnosis, prevention, treatment and follow-up. *Ann Oncol Off J Eur Soc Med Oncol.* 2020;31(10):1306-1319. doi:10.1016/J.ANNONC.2020.07.003
 16. Loprinzi CL, Lacchetti C, Bleeker J, et al. Prevention and Management of Chemotherapy-Induced Peripheral Neuropathy in Survivors of Adult Cancers: ASCO Guideline Update. *J Clin Oncol.* 2020;38(28):3325-3348. doi:10.1200/JCO.20.01399
 17. Albany C, Dockett T, Wolfe E, et al. Cisplatin-associated neuropathy characteristics compared with those associated with other neurotoxic chemotherapy agents (Alliance A151724). *Support Care Cancer.* 2021;29(2):833-840. doi:10.1007/S00520-020-05543-5
 18. Cisplatin-induced peripheral neuropathy. Frequent off-therapy deterioration, demyelinating syndromes, and muscle cramps - PubMed. Accessed October 11, 2022. <https://pubmed.ncbi.nlm.nih.gov/2169332/>
 19. Glendenning JL, Barbachano Y, Norman AR, Dearnaley DP, Horwich A, Huddart RA. Long-term neurologic and peripheral vascular toxicity after chemotherapy treatment of testicular cancer. *Cancer.* 2010;116(10):2322-2331. doi:10.1002/CNCR.24981
 20. Langer T, Am Zehnhoff-Dinnesen A, Radtke S, Meitert J, Zolk O. Understanding platinum-induced ototoxicity. *Trends Pharmacol Sci.* 2013;34(8):458-469. doi:10.1016/J.TIPS.2013.05.006
 21. Calvert AH, Newell DR, Gumbrell LA, et al. Carboplatin dosage: prospective evaluation of a simple formula based on renal function. *J Clin Oncol.* 1989;7(11):1748-1756. doi:10.1200/JCO.1989.7.11.1748
 22. UpToDate. Carboplatin: Drug Information. Published 2022. Accessed October 16, 2022. https://www.uptodate.com/contents/carboplatin-drug-information?search=carboplatin&source=panel_search_result&selectedTitle=1~148&usage_type=panel&kp_tab=drug_general&display_rank=1#F50989309
 23. Iihara H, Shimokawa M, Hayasaki Y, et al. Efficacy and safety of 5 mg olanzapine combined with aprepitant, granisetron and dexamethasone to prevent carboplatin-induced nausea and vomiting in patients with gynecologic cancer: A multi-institution phase II study. *Gynecol Oncol.* 2020;156(3):629-635. doi:10.1016/J.YGYNO.2020.01.004
 24. Tanaka K, Inui N, Karayama M, et al. Olanzapine-containing antiemetic therapy for the prevention of carboplatin-induced nausea and vomiting. *Cancer Chemother Pharmacol.* 2019;84(1):147-153. doi:10.1007/S00280-019-03868-5
 25. Di Maio M, Barattelli C, Bironzo P, et al. Efficacy of neurokinin-1 receptor antagonists in the

- prevention of chemotherapy-induced nausea and vomiting in patients receiving carboplatin-based chemotherapy: A systematic review and meta-analysis. *Crit Rev Oncol Hematol*. 2018;124:21-28. doi:10.1016/J.CRITREVO.2018.02.001
26. UpToDate. Chemotherapy nephrotoxicity and dose modification in patients with kidney impairment: Conventional cytotoxic agents. Published 2022. [https://www.uptodate.com/contents/chemotherapy-nephrotoxicity-and-dose-modification-in-patients-with-kidney-impairment-conventional-cytotoxic-agents?search=carboplatin related nephrotoxicity&source=search_result&selectedTitle=1~150&usage_type=default&disp](https://www.uptodate.com/contents/chemotherapy-nephrotoxicity-and-dose-modification-in-patients-with-kidney-impairment-conventional-cytotoxic-agents?search=carboplatin%20related%20nephrotoxicity&source=search_result&selectedTitle=1~150&usage_type=default&disp)
 27. André T, Boni C, Mounedji-Boudiaf L, et al. Oxaliplatin, fluorouracil, and leucovorin as adjuvant treatment for colon cancer. *N Engl J Med*. 2004;350(23):2343-2351. doi:10.1056/NEJM0A032709
 28. André T, Tournigand C, Rosmorduc O, et al. Gemcitabine combined with oxaliplatin (GEMOX) in advanced biliary tract adenocarcinoma: a GERCOR study. *Ann Oncol Off J Eur Soc Med Oncol*. 2004;15(9):1339-1343. doi:10.1093/ANNONC/MDH351
 29. Conroy T, Desseigne F, Ychou M, et al. FOLFIRINOX versus gemcitabine for metastatic pancreatic cancer. *N Engl J Med*. 2011;364(19):1817-1825. doi:10.1056/NEJM0A1011923
 30. André T, Boni C, Navarro M, et al. Improved overall survival with oxaliplatin, fluorouracil, and leucovorin as adjuvant treatment in stage II or III colon cancer in the MOSAIC trial. *J Clin Oncol*. 2009;27(19):3109-3116. doi:10.1200/JCO.2008.20.6771
 31. Bang YJ, Kim YW, Yang HK, et al. Adjuvant capecitabine and oxaliplatin for gastric cancer after D2 gastrectomy (CLASSIC): a phase 3 open-label, randomised controlled trial. *Lancet (London, England)*. 2012;379(9813):315-321. doi:10.1016/S0140-6736(11)61873-4
 32. Synold TW, Takimoto CH, Doroshow JH, et al. Dose-escalating and pharmacologic study of oxaliplatin in adult cancer patients with impaired hepatic function: a National Cancer Institute Organ Dysfunction Working Group study. *Clin Cancer Res*. 2007;13(12):3660-3666. doi:10.1158/1078-0432.CCR-06-2385
 33. Argyriou AA, Cavaletti G, Briani C, et al. Clinical pattern and associations of oxaliplatin acute neurotoxicity: a prospective study in 170 patients with colorectal cancer. *Cancer*. 2013;119(2):438-444. doi:10.1002/CNCR.27732
 34. Pachman DR, Qin R, Seisler DK, et al. Clinical Course of Oxaliplatin-Induced Neuropathy: Results From the Randomized Phase III Trial N08CB (Alliance). *J Clin Oncol*. 2015;33(30):3416-3422. doi:10.1200/JCO.2014.58.8533
 35. Petrioli R, Pascucci A, Francini E, et al. Neurotoxicity of FOLFOX-4 as adjuvant treatment for patients with colon and gastric cancer: a randomized study of two different schedules of oxaliplatin. *Cancer Chemother Pharmacol*. 2008;61(1):105-111. doi:10.1007/S00280-007-0454-3
 36. Cassidy J, Misset J-L. Oxaliplatin-related side effects: characteristics and management. *Semin Oncol*. 2002;29(5 Suppl 15):11-20. doi:10.1053/SONC.2002.35524
 37. de Gramont A, Figer A, Seymour M, et al. Leucovorin and fluorouracil with or without oxaliplatin as first-line treatment in advanced colorectal cancer. *J Clin Oncol*. 2000;18(16):2938-2947. doi:10.1200/JCO.2000.18.16.2938
 38. Bennett BK, Park SB, Lin CSY, Friedlander ML, Kiernan MC, Goldstein D. Impact of oxaliplatin-induced neuropathy: a patient perspective. *Support Care Cancer*. 2012;20(11):2959-2967. doi:10.1007/S00520-012-1428-5
 39. Loprinzi CL, Lacchetti C, Bleeker J, et al. Prevention and Management of Chemotherapy-Induced Peripheral Neuropathy in Survivors of Adult Cancers: ASCO Guideline Update. *J Clin Oncol*. 2020;38(28):3325-3348. doi:10.1200/JCO.20.01399
 40. UpToDate. Oxaliplatin: Drug information. Published 2022. Accessed October 16, 2022. https://www.uptodate.com/contents/oxaliplatin-drug-information?search=oxaliplatin&source=panel_search_result&selectedTitle=1~148&usage_type=panel&kp_tab=drug_general&display_rank=1#F204234
 41. Seo AN a., Kim H. Sinusoidal obstruction syndrome after oxaliplatin-based chemotherapy. *Clin Mol Hepatol*. 2014;20(1):81-84. doi:10.3350/CMH.2014.20.1.81