

BÖLÜM 11

ALKİLLEYİCİ AJANLARIN KLİNİK KULLANIMLARI VE YAN ETKİ YÖNETİMLERİ

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GİRİŞ

İlk keşfedilen antineoplastik ilaçlar olan alkilleyici ajanlar 60 yıldan uzun süredir kanser tedavisinde kullanılmakta olup yeni alkilleyici ajanların keşfiyle beraber kullanım alanları genişlemektedir. Alkilleyici ajanlar hematopoetik kök hücre transplantasyonundan akciğer, meme, over, multiple miyelom ve sarkoma kadar değişik kanser tiplerinde sıklıkla kombinasyon tedavisi olarak yer almaktadır. Klinik kullanım alanı geniş olan siklofosamid en çok kullanılan alkilleyici ajandır (1).

KLİNİK KULLANIM ALANLARI

1.1 Azotlu Hardallar

1.1.1 Klorambusil

Klorambusilin kronik lenfositik lösemide rituksimab ile kombine kullanımı (2) mevcuttur.

1.1.2 Melfalan

Transplantasyona uygun olmayan veya 65 yaş üzerindeki multiple miyelom vakalarında daratumab/hyaluronidaz, bortezomib ve prednizon ile kombine kullanılmaktadır (3). Yüksek doz melfalan tedavisini takiben otolog kök hücre transplantasyonu ise 70 yaş altındaki multiple miyelom hastalarında tercih edilmektedir (4).

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KAYNAKLAR

1. Sensenbrenner LL, Marini JJ, Colvin M. Comparative effects of cyclophosphamide, isophosphamide, 4-methylcyclophosphamide, and phosphoramidate mustard on murine hematopoietic and immunocompetent cells. *J Natl Cancer Inst.* 1979;62(4):975-81.
2. Hillmen P, Gribben JG, Follows GA, Milligan D, Sayala HA, Moreton P, et al. Rituximab plus chlorambucil as first-line treatment for chronic lymphocytic leukemia: final analysis of an open-label phase II study. *Journal of clinical oncology.* 2014;32(12):1236.
3. Chari A, Rodriguez-Otero P, McCarthy H, Suzuki K, Hungria V, Sureda Balari A, et al. Subcutaneous daratumumab plus standard treatment regimens in patients with multiple myeloma across lines of therapy (PLEIADES): an open-label Phase II study. *Br J Haematol.* 2021;192(5):869-78.
4. Becker N. Epidemiology of multiple myeloma. *Recent Results Cancer Res.* 2011;183:25-35.
5. Diehl V, Franklin J, Pfreundschuh M, Lathan B, Paulus U, Hasenclever D, et al. Standard and increased-dose BEACOPP chemotherapy compared with COPP-ABVD for advanced Hodgkin's disease. *New England Journal of Medicine.* 2003;348(24):2386-95.
6. Fisher RI, Gaynor ER, Dahlborg S, Oken MM, Grogan TM, Mize EM, et al. Comparison of a standard regimen (CHOP) with three intensive chemotherapy regimens for advanced non-Hodgkin's lymphoma. *New England Journal of Medicine.* 1993;328(14):1002-6.
7. DeFilipp Z, Li S, El-Jawahri A, Armand P, Nayak L, Wang N, et al. High-dose chemotherapy with thiotepa, busulfan, and cyclophosphamide and autologous stem cell transplantation for patients with primary central nervous system lymphoma in first complete remission. *Cancer.* 2017;123(16):3073-9.
8. Keating MJ, O'Brien S, Albitar M, Lerner S, Plunkett W, Giles F, et al. Early results of a chemotherapeutic regimen of fludarabine, cyclophosphamide, and rituximab as initial therapy for chronic lymphocytic leukemia. *Journal of clinical oncology.* 2005;23(18):4079-88.
9. Wierda W, O'Brien S, Wen S, Faderl S, Garcia-Manero G, Thomas D, et al. Chemoimmunotherapy with fludarabine, cyclophosphamide, and rituximab for relapsed and refractory chronic lymphocytic leukemia. *Journal of clinical oncology.* 2005;23(18):4070-8.
10. Stock W, Luger SM, Advani AS, Yin J, Harvey RC, Mullighan CG, et al. A pediatric regimen for older adolescents and young adults with acute lymphoblastic leukemia: results of CALGB 10403. *Blood, The Journal of the American Society of Hematology.* 2019;133(14):1548-59.
11. Ravandi F, O'Brien S, Thomas D, Faderl S, Jones D, Garris R, et al. First report of phase 2 study of dasatinib with hyper-CVAD for the frontline treatment of patients with Philadelphia chromosome-positive (Ph+) acute lymphoblastic leukemia. *Blood, The Journal of the American Society of Hematology.* 2010;116(12):2070-7.
12. Cassileth PA, Harrington DP, Appelbaum FR, Lazarus HM, Rowe JM, Paietta E, et al. Chemotherapy compared with autologous or allogeneic bone marrow transplantation in the management of acute myeloid leukemia in first remission. *New England Journal of Medicine.* 1998;339(23):1649-56.
13. Khouri IF, McLaughlin P, Saliba RM, Hosing C, Korbling M, Lee MS, et al. Eight-year experience with allogeneic stem cell transplantation for relapsed follicular lymphoma after nonmyeloablative conditioning with fludarabine, cyclophosphamide, and rituximab. *Blood, The Journal of the American Society of Hematology.* 2008;111(12):5530-6.
14. Grier HE, Kralo MD, Tarbell NJ, Link MP, Fryer CJ, Pritchard DJ, et al. Addition of ifosfamide and etoposide to standard chemotherapy for Ewing's sarcoma and primitive neuroectodermal tumor of bone. *New England Journal of Medicine.* 2003;348(8):694-701.
15. Arndt CA, Stoner JA, Hawkins DS, Rodeberg DA, Hayes-Jordan AA, Pavidas CN, et al. Vincristine, actinomycin, and cyclophosphamide compared with vincristine, actinomycin, and cyclophosphamide alternating with vincristine, topotecan, and cyclophosphamide for intermediate-risk rhabdomyosarcoma: children's oncology group study D9803. *Journal of Clinical Oncology.* 2009;27(31):5182.

16. Fenig E, Brenner B, Katz A, Rakovsky E, Hana MB, Sulkes A. The role of radiation therapy and chemotherapy in the treatment of Merkel cell carcinoma. *Cancer: Interdisciplinary International Journal of the American Cancer Society*. 1997;80(5):881-5.
17. Fisher B, Brown AM, Dimitrov NV, Poisson R, Redmond C, Margolese RG, et al. Two months of doxorubicin-cyclophosphamide with and without interval reinduction therapy compared with 6 months of cyclophosphamide, methotrexate, and fluorouracil in positive-node breast cancer patients with tamoxifen-nonresponsive tumors: results from the National Surgical Adjuvant Breast and Bowel Project B-15. *Journal of Clinical Oncology*. 1990;8(9):1483-96.
18. Martin M, Pienkowski T, Mackey J, Pawlicki M, Guastalla J-P, Weaver C, et al. Adjuvant docetaxel for node-positive breast cancer. *New England Journal of Medicine*. 2005;352(22):2302-13.
19. Worden FP, Taylor J, Biermann JS, Sondak VK, Leu KM, Chugh R, et al. Randomized Phase II Evaluation of 6 g/m² of Ifosfamide Plus Doxorubicin and Granulocyte Colony-Stimulating Factor(G-CSF) Compared With 12 g/m² of Ifosfamide Plus Doxorubicin and G-CSF in the Treatment of Poor-Prognosis Soft Tissue Sarcoma. *Journal of Clinical Oncology*. 2004;23(1):105-12.
20. Nichols CR, Catalano PJ, Crawford ED, Vogelzang NJ, Einhorn LH, Loehrer PJ. Randomized comparison of cisplatin and etoposide and either bleomycin or ifosfamide in treatment of advanced disseminated germ cell tumors: an Eastern Cooperative Oncology Group, Southwest Oncology Group, and Cancer and Leukemia Group B Study. *Journal of Clinical Oncology*. 1998;16(4):1287-93.
21. Mead GM, Barrans SL, Qian W, Walewski J, Radford JA, Wolf M, et al. A prospective clinicopathologic study of dose-modified CODOX-M/IVAC in patients with sporadic Burkitt lymphoma defined using cytogenetic and immunophenotypic criteria (MRC/NCRI LY10 trial). *Blood, The Journal of the American Society of Hematology*. 2008;112(6):2248-60.
22. Brandes A, Tosoni A, Amista P, Nicolardi L, Grosso D, Berti F, et al. How effective is BCNU in recurrent glioblastoma in the modern era?: A phase II trial. *Neurology*. 2004;63(7):1281-4.
23. Group BTC, Selker RG, Shapiro WR, Burger P, Blackwood MS, Deutsch M, et al. The Brain Tumor Cooperative Group NIH Trial 87-01: a randomized comparison of surgery, external radiotherapy, and carmustine versus surgery, interstitial radiotherapy boost, external radiation therapy, and carmustine. *Neurosurgery*. 2002;51(2):343-57.
24. Levin VA, Uhm JH, Jaeckle KA, Choucair A, Flynn PJ, Yung WKA, et al. Phase III randomized study of postradiotherapy chemotherapy with alpha-difluoromethylornithine-procarbazine, N-(2-chloroethyl)-N'-cyclohexyl-N-nitrosourea, vincristine (DFMO-PCV) versus PCV for glioblastoma multiforme. *Clin Cancer Res*. 2000;6(10):3878-84.
25. Buckner JC, Shaw EG, Pugh SL, Chakravarti A, Gilbert MR, Barger GR, et al. Radiation plus Procarbazine, CCNU, and Vincristine in Low-Grade Glioma. *N Engl J Med*. 2016;374(14):1344-55.
26. Moertel CG, Lefkopoulo M, Lipsitz S, Hahn RG, Klaassen D. Streptozocin-doxorubicin, streptozocin-fluorouracil, or chlorozotocin in the treatment of advanced islet-cell carcinoma. *New England Journal of Medicine*. 1992;326(8):519-23.
27. Fassnacht M, Terzolo M, Allolio B, Baudin E, Haak H, Berruti A, et al. Combination chemotherapy in advanced adrenocortical carcinoma. *N Engl J Med*. 2012;366(23):2189-97.
28. Middleton MR, Grob JJ, Aaronson N, Fierlbeck G, Tilgen W, Seiter S, et al. Randomized phase III study of temozolomide versus dacarbazine in the treatment of patients with advanced metastatic malignant melanoma. *J Clin Oncol*. 2000;18(1):158-66.
29. Engert A, Franklin J, Eich HT, Brillant C, Sehlen S, Cartoni C, et al. Two cycles of doxorubicin, bleomycin, vinblastine, and dacarbazine plus extended-field radiotherapy is superior to radiotherapy alone in early favorable Hodgkin's lymphoma: final results of the GHSG HD7 trial. *J Clin Oncol*. 2007;25(23):3495-502.
30. Omuro A, Chan TA, Abrey LE, Khasraw M, Reiner AS, Kaley TJ, et al. Phase II trial of continuous low-dose temozolomide for patients with recurrent malignant glioma. *Neuro Oncol*. 2013;15(2):242-50.

31. Hegi ME, Diserens A-C, Gorlia T, Hamou M-F, De Tribolet N, Weller M, et al. MGMT gene silencing and benefit from temozolomide in glioblastoma. *New England Journal of Medicine*. 2005;352(10):997-1003.
32. Fischer K, Cramer P, Busch R, Böttcher S, Bahlo J, Schubert J, et al. Bendamustine in combination with rituximab for previously untreated patients with chronic lymphocytic leukemia: a multicenter phase II trial of the German Chronic Lymphocytic Leukemia Study Group. *J Clin Oncol*. 2012;30(26):3209-16.
33. Scott BL, Pasquini MC, Logan BR, Wu J, Devine SM, Porter DL, et al. Myeloablative Versus Reduced-Intensity Hematopoietic Cell Transplantation for Acute Myeloid Leukemia and Myelodysplastic Syndromes. *J Clin Oncol*. 2017;35(11):1154-61.
34. Jabbour E, Kantarjian H. Chronic myeloid leukemia: 2020 update on diagnosis, therapy and monitoring. *Am J Hematol*. 2020;95(6):691-709.
35. Soussain C, Hoang-Xuan K, Taillandier L, Fourme E, Choquet S, Witz F, et al. Intensive chemotherapy followed by hematopoietic stem-cell rescue for refractory and recurrent primary CNS and intraocular lymphoma: Société Française de Greffe de Moëlle Osseuse-Thérapie Cellulaire. *J Clin Oncol*. 2008;26(15):2512-8.
36. Grossman SA, Finkelstein DM, Ruckdeschel JC, Trump DL, Moynihan T, Ettinger DS. Randomized prospective comparison of intraventricular methotrexate and thiotepa in patients with previously untreated neoplastic meningitis. Eastern Cooperative Oncology Group. *J Clin Oncol*. 1993;11(3):561-9.
37. Demetri GD, von Mehren M, Jones RL, Hensley ML, Schuetze SM, Staddon A, et al. Efficacy and Safety of Trabectedin or Dacarbazine for Metastatic Liposarcoma or Leiomyosarcoma After Failure of Conventional Chemotherapy: Results of a Phase III Randomized Multicenter Clinical Trial. *J Clin Oncol*. 2016;34(8):786-93.
38. Trigo J, Subbiah V, Besse B, Moreno V, López R, Sala MA, et al. Lurbinectedin as second-line treatment for patients with small-cell lung cancer: a single-arm, open-label, phase 2 basket trial. *Lancet Oncol*. 2020;21(5):645-54.
39. Mendiola C, Valdiviezo N, Vega E, Sanchez Munoz A, Ciruelos EM, Manso L, et al. Altrexamine for recurrent ovarian cancer or as maintenance after response to second-line therapy. *Journal of Clinical Oncology*. 2011;29(15_suppl):e15589-e.
40. Petrylak DP, Tangen CM, Hussain MH, Lara Jr PN, Jones JA, Taplin ME, et al. Docetaxel and estramustine compared with mitoxantrone and prednisone for advanced refractory prostate cancer. *New England Journal of Medicine*. 2004;351(15):1513-20.
41. Lazarus HM, Phillips GL, Herzig RH, Hurd DD, Wolff SN, Herzig GP. High-dose melphalan and the development of hematopoietic stem-cell transplantation: 25 years later. *Journal of Clinical Oncology*. 2008;26(14):2240-3.
42. Aisa Y, Mori T, Kudo M, Yashima T, Kondo S, Yokoyama A, et al. Oral cryotherapy for the prevention of high-dose melphalan-induced stomatitis in allogeneic hematopoietic stem cell transplant recipients. *Support Care Cancer*. 2005;13(4):266-9.
43. Colvin M, Russo JE, Hilton J, Dulik DM, Fenselau C. Enzymatic mechanisms of resistance to alkylating agents in tumor cells and normal tissues. *Adv Enzyme Regul*. 1988;27:211-21.
44. De Jonge M, Huitema A, Beijnen J, Rodenhuis S. High exposures to bioactivated cyclophosphamide are related to the occurrence of veno-occlusive disease of the liver following high-dose chemotherapy. *British journal of cancer*. 2006;94(9):1226-30.
45. Warr D. Management of highly emetogenic chemotherapy. *Current Opinion in Oncology*. 2012;24(4):371-5.
46. Hesketh PJ, Kris MG, Basch E, Bohlke K, Barbour SY, Clark-Snow RA, et al. Antiemetics: ASCO Guideline Update. *Journal of Clinical Oncology*. 2020;38(24):2782-97.
47. Viaud S, Saccheri F, Mignot G, Yamazaki T, Daillère R, Hannani D, et al. The intestinal microbiota modulates the anticancer immune effects of cyclophosphamide. *Science*. 2013;342(6161):971-6.
48. Samuels BL, Bitran JD. High-dose intravenous melphalan: a review. *Journal of clinical oncology*. 1995;13(7):1786-99.

49. Fraiser LH, Kanekal S, Kehrer JP. Cyclophosphamide toxicity. *Drugs*. 1991;42(5):781-95.
50. Avilés A, Díaz-Maqueo JC, Talavera A, García EL, Guzmán R, Nambo MJ. Bone marrow protection with amifostine in the treatment of high-risk malignant lymphoma. *Eur J Cancer*. 1997;33(8):1323-5.
51. Huitema AD, Smits KD, Mathôt RA, Schellens JH, Rodenhuis S, Beijnen JH. The clinical pharmacology of alkylating agents in high-dose chemotherapy. *Anti-Cancer Drugs*. 2000;11(7):515-33.
52. Cantrell JE, Jr., Green D, Schein PS. Antitumor activity and bone marrow toxicity of aminoglucose mustard anticancer agents in mice. *Cancer Res*. 1986;46(5):2340-3.
53. Stillwell TJ, Benson Jr RC. Cyclophosphamide-induced hemorrhagic cystitis: a review of 100 patients. *Cancer*. 1988;61(3):451-7.
54. Cox PJ. Cyclophosphamide cystitis—identification of acrolein as the causative agent. *Biochemical pharmacology*. 1979;28(13):2045-9.
55. Haselberger MB, Schwinghammer TL. Efficacy of mesna for prevention of hemorrhagic cystitis after high-dose cyclophosphamide therapy. *Annals of Pharmacotherapy*. 1995;29(9):918-21.
56. Apperley J, Rice S, Bishop J, Chia Y, Krausz T, Gardner S, et al. Late-onset hemorrhagic cystitis associated with urinary excretion of polyomaviruses after bone marrow transplantation. *Transplantation*. 1987;43(1):108-12.
57. Bedi A, Miller CB, Hanson JL, Goodman S, Ambinder RF, Charache P, et al. Association of BK virus with failure of prophylaxis against hemorrhagic cystitis following bone marrow transplantation. *Journal of Clinical Oncology*. 1995;13(5):1103-9.
58. Miyamura K. Adenovirus-induced hemorrhagic cystitis following allogeneic bone marrow transplantation. *Bone Marrow Transplantation*. 1987;2:109-15.
59. Vlaovic P, Jewett M. Cyclophosphamide-induced bladder cancer. *The Canadian Journal of Urology*. 1999;6(2):745-8.
60. Blumenfeld Z. Chemotherapy and fertility. *Best practice & research Clinical obstetrics & gynaecology*. 2012;26(3):379-90.
61. High-Dose Alkylating Agent Therapy: A Review of Clinical Experiences. *Cancer Drug Delivery*. 1984;1(3):227-38.
62. Miller DG. Alkylating Agents and. *JAMA*. 1971;217(12):1662-5.
63. Pai VB, Nahata MC. Cardiotoxicity of chemotherapeutic agents. *Drug safety*. 2000;22(4):263-302.
64. Steinherz LJ, Steinherz PG, Mangiacasale D, O'Reilly R, Allen J, Sorell M, et al. Cardiac changes with cyclophosphamide. *Med Pediatr Oncol*. 1981;9(5):417-22.
65. Littler WA, Ogilvie C. Lung function in patients receiving busulphan. *Br Med J*. 1970;4(5734):530-2.
66. Mark GJ, Lehimgar-Zadeh A, Ragsdale BD. Cyclophosphamide pneumonitis. *Thorax*. 1978;33(1):89-93.
67. Neuwelt AJ, Nguyen TM, Fu R, Bubalo J, Tyson RM, Lacy C, et al. Incidence of *Pneumocystis jirovecii* pneumonia after temozolomide for CNS malignancies without prophylaxis. *CNS Oncol*. 2014;3(4):267-73.
68. Cole SR, Myers TJ, Klatsky AU. Pulmonary disease with chlorambucil therapy. *Cancer*. 1978;41(2):455-9.
69. Segura A, Yuste A, Cercos A, López-Tendero P, Gironés R, Pérez-Fidalgo JA, et al. Pulmonary fibrosis induced by cyclophosphamide. *Annals of Pharmacotherapy*. 2001;35(7-8):894-7.
70. Goucher G, Rowland V, Hawkins J. Melphalan-induced pulmonary interstitial fibrosis. *Chest*. 1980;77(6):805-6.
71. Baruchel S, Diezi M, Hargrave D, Stempak D, Gammon J, Moghrabi A, et al. Safety and pharmacokinetics of temozolomide using a dose-escalation, metronomic schedule in recurrent paediatric brain tumours. *Eur J Cancer*. 2006;42(14):2335-42.
72. Pratt CB, Goren MP, Meyer WH, Singh B, Dodge RK. Ifosfamide neurotoxicity is related to previous cisplatin treatment for pediatric solid tumors. *J Clin Oncol*. 1990;8(8):1399-401.

73. Pelgrims J, De Vos F, Van den Brande J, Schrijvers D, Prové A, Vermorken JB. Methylene blue in the treatment and prevention of ifosfamide-induced encephalopathy: report of 12 cases and a review of the literature. *Br J Cancer*. 2000;82(2):291-4.
74. Eberly AL, Anderson GD, Bubalo JS, McCune JS. Optimal prevention of seizures induced by high-dose busulfan. *Pharmacotherapy*. 2008;28(12):1502-10.
75. Nicholson HO. Cytotoxic drugs in pregnancy. Review of reported cases. *J Obstet Gynaecol Br Commonw*. 1968;75(3):307-12.
76. Levine E, Bloomfield C, editors. Leukemias and myelodysplastic syndromes secondary to drug, radiation, and environmental exposure. *Seminars in oncology*; 1992.
77. Calvert W. Alopecia and cytotoxic drugs. *Br Med J*. 1966;2(5517):831.
78. Cigler T, Isseroff D, Fiederlein B, Schneider S, Chuang E, Vahdat L, et al. Efficacy of Scalp Cooling in Preventing Chemotherapy-Induced Alopecia in Breast Cancer Patients Receiving Adjuvant Docetaxel and Cyclophosphamide Chemotherapy. *Clin Breast Cancer*. 2015;15(5):332-4.
79. Reyes-Habito CM, Roh EK. Cutaneous reactions to chemotherapeutic drugs and targeted therapies for cancer: part I. Conventional chemotherapeutic drugs. *J Am Acad Dermatol*. 2014;71(2):203.e1-.e12; quiz 15-6.
80. Weiss RB, Bruno S. Hypersensitivity reactions to cancer chemotherapeutic agents. *Ann Intern Med*. 1981;94(1):66-72.
81. Pérez Fidalgo JA, García Fabregat L, Cervantes A, Margulies A, Vidall C, Roila F. Management of chemotherapy extravasation: ESMO-EONS Clinical Practice Guidelines. *Ann Oncol*. 2012;23 Suppl 7:vii167-73.
82. Santos GW, Sensenbrenner LL, Burke PJ, Colvin M, Owens AH, Jr, Bias WB, et al. Marrow transplantation in man following cyclophosphamide. *Transplant Proc*. 1971;3(1):400-4.
83. Damasceno DC, Netto AO, Iessi IL, Gallego FQ, Corvino SB, Dallaqua B, et al. Streptozotocin-induced diabetes models: pathophysiological mechanisms and fetal outcomes. *Biomed Res Int*. 2014;2014:819065.
84. Campbell DM, Atkinson A, Gillis D, Sochett EB. Cyclophosphamide and water retention: mechanism revisited. *J Pediatr Endocrinol Metab*. 2000;13(6):673-5.
85. Karamanakos PN, Pappas P, Boumba V, Marselos M. Increased Brain Serotonin Rather Than Increased Blood Acetaldehyde as a Common Denominator Behind Alleged Disulfiram-Like Reactions. *Int J Toxicol*. 2020;39(3):248-55.
86. Kraft SL, Baker NM, Carpenter J, Bostwick JR. Procarbazine and antidepressants: a retrospective review of the risk of serotonin toxicity. *Psychooncology*. 2014;23(1):108-13.
87. Collins JM. 25 - Cancer Pharmacology. In: Niederhuber JE, Armitage JO, Kastan MB, Doroshow JH, Tepper JE, editors. *Abeloff's Clinical Oncology (Sixth Edition)*. Philadelphia: Elsevier; 2020. p. 411-9.e44.