Bölüm 27

HEMATOLOJİDE KULLANILAN ORAL KEMOTERAPÖTİKLER

Burak ÖNAL[1]

Oral kemoterapi uygulamaları, 1953'ten beri süregelmektedir. Doksanlı yıllara geçildiğinde, moleküler yapıların daha iyi anlaşılabilir olması ile birlikte, hücre yüzey proteinleri ve tümör ile ilgili yolaklar daha fazla aydınlatılabilir bir hale geldi. Bu yolaklar ve proteinleri hedef alan oral sitotoksik ajanlar ve küçük moleküllü inhibitörler ise giderek genişleyen bir farmakolojik sınıf olan oral kemoterapotikleri oluşturmuştur (Weingart et al., 2008). Oral kemoterapötikler, kullanım ve uygulama kolaylığından dolayı kanser tedavisi için daha popüler hale gelmektedir. Her ne kadar uygulamada kolaylık sağlayan yanları olsa da oral kemoterapötikler, dar bir terapötik indekse sahiptir ve metabolizmaları gıda ve/veya ilaç etkileşimlerinden kolaylıkla etkilenebilir.

Bu bölümde, hematolojide güncel tedavide kullanılan oral kemoterapötik ilaçları; endikasyonları, etki mekanizmaları, farmakokinetik özellikleri, doz aralıkları, ilaç etkileşimleri, özel durumları ve toksisite özellikleri yönünden inceleyeceğiz.

BEKZAROTEN

Bekzaroten, retinoid sınıfı bir oral kemoterapötik ilaçtır. Bekzaroten, kutanöz T hücreli lenfomanın kutanöz manifestasyonlarında en az bir sistemik tedaviye direnç gösteren olgularda endikedir.

Etki mekanizması: Retinoid X reseptörlerine (RXRs) seçici olarak bağlanır ve reseptör aktivasyonu sağlar. Retinoid X reseptörleri, retinoik asit reseptörleri (RARs), vitamin D reseptörleri ve tiroid reseptörleri gibi birçok farklı reseptörle de heterodimer oluşturur. Bu reseptörler aktive olduktan sonra, transkripsiyon faktörü olarak çalışır; sonrasında da hücre farklılaşması, büyümesi ve bölünmesini kontrol eden birçok genin regülasyonunda görev alırlar. Bekzarotenin kutanöz T hücreli lenfomadaki antitümör etkisinin mekanizması ise hala tam olarak aydınlatılamamıştır.

[1] Dr. Öğr. Üyesi, Biruni Üniversitesi Tıp Fakültesi Tıbbi Farmakoloji AD, burakonal@yandex.com

Özel Durumlar: Retinoidlere hipersensitivitesi olan hastalarda kontrendikedir. Ateş, solunum sıkıntısı ve lökositoz açısından hasta takip edilmelidir; çünkü hastaların yaklaşık %25'inde retinoik asit sendromu gelişebilir. Serum trigliserid ve kolesterol seviyeleri yakın takibe alınmalıdır. Tam kan sayımı ve karaciğer fonksiyon testleri monitörize edilmelidir. Gebelik kategorisi D olarak bildirilmiştir.

Toksisite: A vitamini toksisitesi (baş ağrısı, cilt ve müköz membranlarda kuruluk, periferal ödem, mukozit, pruritus ve konjonktüvit), retinoik asit sendromu, terleme, hipotansiyon, flebit, konjestif kalp yetmezliği gözlenebilir. Hastaların yaklaşık %60'ında serum kolesterol ve trigliserid düzeyleri artar. Anksiyete, parestezi, depresyon, konfüzyon ve ajitasyon şeklinde ortaya çıkan santral sinir sistemi toksisitesi gözlenebilir. Gastrointestinal kanama, duyma kaybı, renal disfonksiyon psödotümör serebri gözlenebilir. Teratojenite gözlenebilir (Degos et al., 1995; Estey et al., 2006; Fenaux et al., 1999; Sanz et al., 2010; Zhang et al., 2002)

KAYNAKLAR

Aisner, J., Whitacre, M., Abrams, J., & Propert, K. (1986). Doxorubicin, cyclophosphamide, etoposide and platinum, doxorubicin, cyclophosphamide and etoposide for small-cell carcinoma of the lung. *Semin Oncol, 13*(3 Suppl 3), 54-62.

Bear, H. D., Anderson, S., Brown, A., Smith, R., Mamounas, E. P., Fisher, B., . . . Bowel Project Protocol, B. (2003). The effect on tumor response of adding sequential preoperative docetaxel to preoperative doxorubicin and cyclophosphamide: preliminary results from National Surgical Adjuvant Breast and Bowel Project Protocol B-27. *J Clin Oncol, 21*(22), 4165-4174. doi:10.1200/JCO.2003.12.005

Buchner, T., Hiddemann, W., Wormann, B., Loffler, H., Gassmann, W., Haferlach, T., . . . Heinecke, A. (1999). Double induction strategy for acute myeloid leukemia: the effect of high-dose cytarabine with mitoxantrone instead of standard-dose cytarabine with daunorubicin and 6-thioguanine: a randomized trial by the German AML Cooperative Group. *Blood, 93*(12), 4116-4124.

Buckner, J. C., Gesme, D., Jr., O'Fallon, J. R., Hammack, J. E., Stafford, S., Brown, P. D., . . . Jenkins, R. (2003). Phase II trial of procarbazine, lomustine, and vincristine as initial therapy for patients with low-grade oligodendroglioma or oligoastrocytoma: efficacy and associations with chromosomal abnormalities. *J Clin Oncol, 21*(2), 251-255. doi:10.1200/JCO.2003.06.023

Byrd, J. C., Peterson, B. L., Morrison, V. A., Park, K., Jacobson, R., Hoke, E., . . . Larson, R. A. (2003). Randomized phase 2 study of fludarabine with concurrent versus sequential treatment with rituximab in symptomatic, untreated patients with B-cell chronic lymphocytic leukemia: results from Cancer and Leukemia Group B 9712 (CALGB 9712). *Blood, 101*(1), 6-14. doi:10.1182/blood-2002-04-1258

Canellos, G. P., Gollub, J., Neuberg, D., Mauch, P., & Shulman, L. N. (2003). Primary systemic treatment of advanced Hodgkin's disease with EVA (etoposide, vinblastine, doxorubicin): 10-year follow-up. *Ann Oncol, 14*(2), 268-272.

Degos, L., Dombret, H., Chomienne, C., Daniel, M. T., Miclea, J. M., Chastang, C., . . . Fenaux, P. (1995). All-trans-retinoic acid as a differentiating agent in the treatment of acute promyelocytic leukemia. *Blood, 85*(10), 2643-2653.

Devita, V. T., Jr., Serpick, A. A., & Carbone, P. P. (1970). Combination chemotherapy in the treatment of advanced Hodgkin's disease. *Ann Intern Med, 73*(6), 881-895.

Diehl, V., Franklin, J., Hasenclever, D., Tesch, H., Pfreundschuh, M., Lathan, B., . . . Loeffler, M. (1998). BEACOPP, a new dose-escalated and accelerated regimen, is at least as effective as COPP/ABVD in patients with advanced-stage Hodgkin's lymphoma: interim report from a trial of the German Hodgkin's Lymphoma Study Group. *J Clin Oncol, 16*(12), 3810-3821. doi:10.1200/JCO.1998.16.12.3810

Dighiero, G., Binet, J. J. H., & therapy, c. (1996). Chronic lymphocytic leukemia. *38*(2), S41.

Dighiero, G., Maloum, K., Desablens, B., Cazin, B., Navarro, M., Leblay, R., . . . Travade, P. (1998). Chlorambucil in indolent chronic lymphocytic leukemia. French Cooperative Group on Chronic Lymphocytic Leukemia. *N Engl J Med, 338*(21), 1506-1514. doi:10.1056/NEJM199805213382104

Dohner, H., Estey, E. H., Amadori, S., Appelbaum, F. R., Buchner, T., Burnett, A. K., . . . European, L. (2010). Diagnosis and management of acute myeloid leukemia in adults: recommendations from an international expert panel, on behalf of the European LeukemiaNet. *Blood, 115*(3), 453-474. doi:10.1182/blood-2009-07-235358

Duvic, M., Hymes, K., Heald, P., Breneman, D., Martin, A. G., Myskowski, P., . . . Bexarotene Worldwide Study, G. (2001). Bexarotene is effective and safe for treatment of refractory advanced-stage cutaneous T-cell lymphoma: multinational phase II-III trial results. *J Clin Oncol, 19*(9), 2456-2471. doi:10.1200/JCO.2001.19.9.2456

Eckardt, J. R., von Pawel, J., Papai, Z., Tomova, A., Tzekova, V., Crofts, T. E., . . . Ross, G. (2006). Open-label, multicenter, randomized, phase III study comparing oral topotecan/cisplatin versus etoposide/cisplatin as treatment for chemotherapy-naive patients with extensive-disease small-cell lung cancer. *J Clin Oncol, 24*(13), 2044-2051. doi:10.1200/JCO.2005.03.3332

Estey, E., Garcia-Manero, G., Ferrajoli, A., Faderl, S., Verstovsek, S., Jones, D., & Kantarjian, H. (2006). Use of all-trans retinoic acid plus arsenic trioxide as an alternative to chemotherapy in untreated acute promyelocytic leukemia. *Blood, 107*(9), 3469-3473. doi:10.1182/blood-2005-10-4006

Estlin, E. J. (2001). Continuing therapy for childhood acute lymphoblastic leukaemia: clinical and cellular pharmacology of methotrexate, 6-mercaptopurine and 6-thioguanine. *Cancer Treat Rev, 27*(6), 351-363. doi:10.1053/ctrv.2002.0245

Facon, T., Mary, J. Y., Hulin, C., Benboubker, L., Attal, M., Pegourie, B., . . . Intergroupe Francophone du, M. (2007). Melphalan and prednisone plus thalidomide versus melphalan and prednisone alone or reduced-intensity autologous stem cell transplantation in elderly patients with multiple myeloma (IFM 99-06): a randomised trial. *Lancet, 370*(9594), 1209-1218. doi:10.1016/S0140-6736(07)61537-2

Facon, T., Mary, J. Y., Pegourie, B., Attal, M., Renaud, M., Sadoun, A., . . . Intergroupe Francophone du Myelome, g. (2006). Dexamethasone-based regimens versus melphalan-prednisone for elderly multiple myeloma patients ineligible for high-dose therapy. *Blood, 107*(4), 1292-1298. doi:10.1182/blood-2005-04-1588

Federico, M., Luminari, S., Iannitto, E., Polimeno, G., Marcheselli, L., Montanini, A., . . . Trial, H. D. G. I. p. l. S. d. L. (2009). ABVD compared with BEACOPP compared with CEC for the initial treatment of patients with advanced Hodgkin's lymphoma: re-

sults from the HD2000 Gruppo Italiano per lo Studio dei Linfomi Trial. *J Clin Oncol, 27*(5), 805-811. doi:10.1200/JCO.2008.17.0910

Fenaux, P., Chastang, C., Chevret, S., Sanz, M., Dombret, H., Archimbaud, E., . . . Degos, L. (1999). A randomized comparison of all transretinoic acid (ATRA) followed by chemotherapy and ATRA plus chemotherapy and the role of maintenance therapy in newly diagnosed acute promyelocytic leukemia. The European APL Group. *Blood, 94*(4), 1192-1200.

Glas, M., Happold, C., Rieger, J., Wiewrodt, D., Bahr, O., Steinbach, J. P., . . . Herrlinger, U. (2009). Long-term survival of patients with glioblastoma treated with radiotherapy and lomustine plus temozolomide. *J Clin Oncol, 27*(8), 1257-1261. doi:10.1200/JCO.2008.19.2195

Goede, V., Fischer, K., Busch, R., Engelke, A., Eichhorst, B., Wendtner, C. M., . . . Hallek, M. (2014). Obinutuzumab plus chlorambucil in patients with CLL and coexisting conditions. *N Engl J Med, 370*(12), 1101-1110. doi:10.1056/NEJMoa1313984

Grund, F. M., Armitage, J. O., & Burns, P. (1977). Hydroxyurea in the prevention of the effects of leukostasis in acute leukemia. *Arch Intern Med, 137*(9), 1246-1247.

Hehlmann, R., Heimpel, H., Hasford, J., Kolb, H. J., Pralle, H., Hossfeld, D. K., . . . et al. (1993). Randomized comparison of busulfan and hydroxyurea in chronic myelogenous leukemia: prolongation of survival by hydroxyurea. The German CML Study Group. *Blood, 82*(2), 398-407.

Hehlmann, R., Heimpel, H., Hasford, J., Kolb, H. J., Pralle, H., Hossfeld, D. K., . . . et al. (1994). Randomized comparison of interferon-alpha with busulfan and hydroxyurea in chronic myelogenous leukemia. The German CML Study Group. *Blood, 84*(12), 4064-4077.

Ho, A. D., Lipp, T., Ehninger, G., Illiger, H. J., Meyer, P., Freund, M., & Hunstein, W. (1988). Combination of mitoxantrone and etoposide in refractory acute myelogenous leukemia--an active and well-tolerated regimen. *J Clin Oncol, 6*(2), 213-217. doi:10.1200/JCO.1988.6.2.213

Hoppe, R. T., Kim, Y. H., Horwitz, S., Zic, J. A., & Corona, R. J. U. W., MA: UpToDate. (2015). Treatment of early stage (IA to IIA) mycosis fungoides.

Keating, M. J., O'Brien, S., Albitar, M., Lerner, S., Plunkett, W., Giles, F., . . . Kantarjian, H. (2005). Early results of a chemoimmunotherapy regimen of fludarabine, cyclophosphamide, and rituximab as initial therapy for chronic lymphocytic leukemia. *J Clin Oncol, 23*(18), 4079-4088. doi:10.1200/JCO.2005.12.051

Keating, M. J., O'Brien, S., Lerner, S., Koller, C., Beran, M., Robertson, L. E., . . . Kantarjian, H. (1998). Long-term follow-up of patients with chronic lymphocytic leukemia (CLL) receiving fludarabine regimens as initial therapy. *Blood, 92*(4), 1165-1171.

Khan, M. L., Reeder, C. B., Kumar, S. K., Lacy, M. Q., Reece, D. E., Dispenzieri, A., . . . Keith Stewart, A. (2012). A comparison of lenalidomide/dexamethasone versus cyclophosphamide/lenalidomide/dexamethasone versus cyclophosphamide/bortezomib/dexamethasone in newly diagnosed multiple myeloma. *Br J Haematol, 156*(3), 326-333. doi:10.1111/j.1365-2141.2011.08949.x

Klimo, P., & Connors, J. M. (1985). MOPP/ABV hybrid program: combination chemotherapy based on early introduction of seven effective drugs for advanced Hodgkin's disease. *J Clin Oncol, 3*(9), 1174-1182. doi:10.1200/JCO.1985.3.9.1174

Kumar, S., Flinn, I., Richardson, P. G., Hari, P., Callander, N., Noga, S. J., . . . Rajkumar, S. V. (2012). Randomized, multicenter, phase 2 study (EVOLUTION) of combinations of bortezomib, dexamethasone, cyclophosphamide, and lenalidomide

in previously untreated multiple myeloma. *Blood, 119*(19), 4375-4382. doi:10.1182/blood-2011-11-395749

Landier, W., Hageman, L., Chen, Y., Kornegay, N., Evans, W. E., Bostrom, B. C., . . . Bhatia, S. (2017). Mercaptopurine Ingestion Habits, Red Cell Thioguanine Nucleotide Levels, and Relapse Risk in Children With Acute Lymphoblastic Leukemia: A Report From the Children's Oncology Group Study AALL03N1. *J Clin Oncol, 35*(15), 1730-1736. doi:10.1200/JCO.2016.71.7579

Lange, B. J., Bostrom, B. C., Cherlow, J. M., Sensel, M. G., La, M. K., Rackoff, W., . . . Children's Cancer, G. (2002). Double-delayed intensification improves event-free survival for children with intermediate-risk acute lymphoblastic leukemia: a report from the Children's Cancer Group. *Blood, 99*(3), 825-833.

Larson, R. A. J. U. t. D. (2015). Post-remission therapy for acute myeloid leukemia in younger adults. *18*.

Lauer, S. J., Shuster, J. J., Mahoney, D. H., Jr., Winick, N., Toledano, S., Munoz, L., . . . Camitta, B. M. (2001). A comparison of early intensive methotrexate/mercaptopurine with early intensive alternating combination chemotherapy for high-risk B-precursor acute lymphoblastic leukemia: a Pediatric Oncology Group phase III randomized trial. *Leukemia, 15*(7), 1038-1045.

Levin, V. A., Silver, P., Hannigan, J., Wara, W. M., Gutin, P. H., Davis, R. L., & Wilson, C. B. (1990). Superiority of post-radiotherapy adjuvant chemotherapy with CCNU, procarbazine, and vincristine (PCV) over BCNU for anaplastic gliomas: NCOG 6G61 final report. *Int J Radiat Oncol Biol Phys, 18*(2), 321-324.

Mateos, M. V., Hernandez, J. M., Hernandez, M. T., Gutierrez, N. C., Palomera, L., Fuertes, M., . . . San Miguel, J. F. (2008). Bortezomib plus melphalan and prednisone in elderly untreated patients with multiple myeloma: updated time-to-events results and prognostic factors for time to progression. *Haematologica, 93*(4), 560-565. doi:10.3324/haematol.12106

McLaughlin, P., Hagemeister, F. B., Romaguera, J. E., Sarris, A. H., Pate, O., Younes, A., . . . Cabanillas, F. (1996). Fludarabine, mitoxantrone, and dexamethasone: an effective new regimen for indolent lymphoma. *J Clin Oncol, 14*(4), 1262-1268. doi:10.1200/JCO.1996.14.4.1262

Montillo, M., Mirto, S., Petti, M. C., Latagliata, R., Magrin, S., Pinto, A., . . . Ferrara, F. (1998). Fludarabine, cytarabine, and G-CSF (FLAG) for the treatment of poor risk acute myeloid leukemia. *Am J Hematol, 58*(2), 105-109.

Moskowitz, C. H., Bertino, J. R., Glassman, J. R., Hedrick, E. E., Hunte, S., Coady-Lyons, N., . . . Zelenetz, A. D. (1999). Ifosfamide, carboplatin, and etoposide: a highly effective cytoreduction and peripheral-blood progenitor-cell mobilization regimen for transplant-eligible patients with non-Hodgkin's lymphoma. *J Clin Oncol, 17*(12), 3776-3785. doi:10.1200/JCO.1999.17.12.3776

O'Brien, S., Kantarjian, H., Beran, M., Smith, T., Koller, C., Estey, E., . . . Keating, M. (1993). Results of fludarabine and prednisone therapy in 264 patients with chronic lymphocytic leukemia with multivariate analysis-derived prognostic model for response to treatment. *Blood, 82*(6), 1695-1700.

Palumbo, A., Bringhen, S., Caravita, T., Merla, E., Capparella, V., Callea, V., . . . Galli, M. J. T. L. (2006). Oral melphalan and prednisone chemotherapy plus thalidomide compared with melphalan and prednisone alone in elderly patients with multiple myeloma: randomised controlled trial. *367*(9513), 825-831.

Palumbo, A., Bringhen, S., Petrucci, M. T., Musto, P., Rossini, F., Nunzi, M., . . . Bocca-

doro, M. (2004). Intermediate-dose melphalan improves survival of myeloma patients aged 50 to 70: results of a randomized controlled trial. *Blood, 104*(10), 3052-3057. doi:10.1182/blood-2004-02-0408

Radhakrishnan, V., Perumal, J., Sundersingh, S., & Sagar, T. (2017). Lomustine induced acute pulmonary toxicity in a pediatric medulloblastoma survivor. *South Asian J Cancer, 6*(1), 38-39. doi:10.4103/2278-330X.202570

Raphael, B., Andersen, J. W., Silber, R., Oken, M., Moore, D., Bennett, J., . . . et al. (1991). Comparison of chlorambucil and prednisone versus cyclophosphamide, vincristine, and prednisone as initial treatment for chronic lymphocytic leukemia: long-term follow-up of an Eastern Cooperative Oncology Group randomized clinical trial. *J Clin Oncol, 9*(5), 770-776. doi:10.1200/JCO.1991.9.5.770

Reif, S., Nicolson, M. C., Bisset, D., Reid, M., Kloft, C., Jaehde, U., & McLeod, H. L. J. E. j. o. c. p. (2002). Effect of grapefruit juice intake on etoposide bioavailability. *58*(7), 491-494.

Riccardi, R., Balis, F. M., Ferrara, P., Lasorella, A., Poplack, D. G., & Mastrangelo, R. (1986). Influence of food intake on bioavailability of oral 6-mercaptopurine in children with acute lymphoblastic leukemia. *Pediatr Hematol Oncol, 3*(4), 319-324.

Rodriguez, M. A., Cabanillas, F. C., Hagemeister, F. B., McLaughlin, P., Romaguera, J. E., Swan, F., & Velasquez, W. (1995). A phase II trial of mesna/ifosfamide, mitoxantrone and etoposide for refractory lymphomas. *Ann Oncol, 6*(6), 609-611.

Roth, B. J., Johnson, D. H., Einhorn, L. H., Schacter, L. P., Cherng, N. C., Cohen, H. J., . . . et al. (1992). Randomized study of cyclophosphamide, doxorubicin, and vincristine versus etoposide and cisplatin versus alternation of these two regimens in extensive small-cell lung cancer: a phase III trial of the Southeastern Cancer Study Group. *J Clin Oncol, 10*(2), 282-291. doi:10.1200/JCO.1992.10.2.282

Russi, E. W., Negrin, R. S., Jett, J. R., Savarese, D. M. J. U. i. p., & Society, c. c. m. A. T. (2000). Busulfan-induced pulmonary injury. *8*.

Sacchi, S., Pozzi, S., Marcheselli, R., Federico, M., Tucci, A., Merli, F., . . . Italian Lymphoma Study, G. (2007). Rituximab in combination with fludarabine and cyclophosphamide in the treatment of patients with recurrent follicular lymphoma. *Cancer, 110*(1), 121-128. doi:10.1002/cncr.22740

Sanz, M. A., Montesinos, P., Rayon, C., Holowiecka, A., de la Serna, J., Milone, G., . . . Groups, H. (2010). Risk-adapted treatment of acute promyelocytic leukemia based on all-trans retinoic acid and anthracycline with addition of cytarabine in consolidation therapy for high-risk patients: further improvements in treatment outcome. *Blood, 115*(25), 5137-5146. doi:10.1182/blood-2010-01-266007

Sawitsky, A., Rai, K. R., Glidewell, O., & Silver, R. T. (1977). Comparison of daily versus intermittent chlorambucil and prednisone therapy in the treatment of patients with chronic lymphocytic leukemia. *Blood, 50*(6), 1049-1059.

Shaye, O. A., Yadegari, M., Abreu, M. T., Poordad, F., Simon, K., Martin, P., . . . Tran, T. T. (2007). Hepatotoxicity of 6-mercaptopurine (6-MP) and Azathioprine (AZA) in adult IBD patients. *Am J Gastroenterol, 102*(11), 2488-2494. doi:10.1111/j.1572-0241.2007.01515.x

Singh, F., & Lebwohl, M. G. (2004). Cutaneous T-cell lymphoma treatment using bexarotene and PUVA: a case series. *J Am Acad Dermatol, 51*(4), 570-573. doi:10.1016/j.jaad.2003.05.010

Szumlanski, C. L., & Weinshilboum, R. M. (1995). Sulphasalazine inhibition of thiopurine methyltransferase: possible mechanism for interaction with 6-mercaptopurine and

azathioprine. *Br J Clin Pharmacol, 39*(4), 456-459.

Taal, W., Oosterkamp, H. M., Walenkamp, A. M., Dubbink, H. J., Beerepoot, L. V., Hanse, M. C., . . . van den Bent, M. J. (2014). Single-agent bevacizumab or lomustine versus a combination of bevacizumab plus lomustine in patients with recurrent glioblastoma (BELOB trial): a randomised controlled phase 2 trial. *Lancet Oncol, 15*(9), 943-953. doi:10.1016/S1470-2045(14)70314-6

Tesch, H., Diehl, V., Lathan, B., Hasenclever, D., Sieber, M., Ruffer, U., . . . Loeffler, M. (1998). Moderate dose escalation for advanced stage Hodgkin's disease using the bleomycin, etoposide, adriamycin, cyclophosphamide, vincristine, procarbazine, and prednisone scheme and adjuvant radiotherapy: a study of the German Hodgkin's Lymphoma Study Group. *Blood, 92*(12), 4560-4567.

Vora, A., Mitchell, C. D., Lennard, L., Eden, T. O., Kinsey, S. E., Lilleyman, J., . . . National Cancer Research Network Childhood Leukaemia Working, P. (2006). Toxicity and efficacy of 6-thioguanine versus 6-mercaptopurine in childhood lymphoblastic leukaemia: a randomised trial. *Lancet, 368*(9544), 1339-1348. doi:10.1016/S0140-6736(06)69558-5

Wattel, E., Guerci, A., Hecquet, B., Economopoulos, T., Copplestone, A., Mahe, B., . . . Fenaux, P. (1996). A randomized trial of hydroxyurea versus VP16 in adult chronic myelomonocytic leukemia. Groupe Francais des Myelodysplasies and European CMML Group. *Blood, 88*(7), 2480-2487.

Weingart, S. N., Brown, E., Bach, P. B., Eng, K., Johnson, S. A., Kuzel, T. M., . . . Walters, R. S. (2008). NCCN Task Force Report: Oral chemotherapy. *J Natl Compr Canc Netw, 6 Suppl 3*, S1-14.

Whitney, C. W., Sause, W., Bundy, B. N., Malfetano, J. H., Hannigan, E. V., Fowler, W. C., Jr., . . . Liao, S. Y. (1999). Randomized comparison of fluorouracil plus cisplatin versus hydroxyurea as an adjunct to radiation therapy in stage IIB-IVA carcinoma of the cervix with negative para-aortic lymph nodes: a Gynecologic Oncology Group and Southwest Oncology Group study. *J Clin Oncol, 17*(5), 1339-1348. doi:10.1200/JCO.1999.17.5.1339

Wierda, W. G., Kipps, T. J., Mayer, J., Stilgenbauer, S., Williams, C. D., Hellmann, A., . . . Hx, C. D. S. I. (2010). Ofatumumab as single-agent CD20 immunotherapy in fludarabine-refractory chronic lymphocytic leukemia. *J Clin Oncol, 28*(10), 1749-1755. doi:10.1200/JCO.2009.25.3187

Woyach, J. A., Ruppert, A. S., Heerema, N. A., Peterson, B. L., Gribben, J. G., Morrison, V. A., . . . Byrd, J. C. (2011). Chemoimmunotherapy with fludarabine and rituximab produces extended overall survival and progression-free survival in chronic lymphocytic leukemia: long-term follow-up of CALGB study 9712. *J Clin Oncol, 29*(10), 1349-1355. doi:10.1200/JCO.2010.31.1811

Zhang, X., Zhou, H., Wang, J., Yang, L., Hu, Y., Shen, G., . . . Song, S. (2002). Arsenic trioxide, retinoic acid and Ara-c regulated the expression of annexin II on the surface of APL cells, a novel co-receptor for plasminogen/tissue plasminogen activator. *Thromb Res, 106*(1), 63-70.

Zhou, B., Liu, X., Mo, X., Xue, L., Darwish, D., Qiu, W., . . . Yen, Y. J. C. r. (2003). The human ribonucleotide reductase subunit hRRM2 complements p53R2 in response to UV-induced DNA repair in cells with mutant p53. *63*(20), 6583-6594.