Bölüm 1

DİFFÜZ BÜYÜK B HÜCRELİ LENFOMA

Sude Hatun AKTİMUR[1]

EPİDEMİYOLOJİ

Diffüz büyük B hücreli lenfoma (DBBHL) gelişmiş ülkelerde Non-Hodgkin Lenfoma (NHL) vakalarının yaklaşık %25 oran ile en yaygın histolojik alt tipidir (1, 2). DBBHL'nın oldukça heterojen morfolojik, genetik ve biyolojik davranış tarzına sahip olduğu bilinmektedir. USA ve İngiltere'de yaklaşık olarak her yıl 100.000'de 7 yeni vaka bildirilmektedir (3). Tüm Avrupa'da yaklaşık 100.000 vakada 4.92 oranda görülmektedir (4). Diğer NHL'larda olduğu gibi %55 oranda erkek cinsiyette daha fazla görülmektedir. İnsidans yaşla birlikte artar, tanı için median yaş 64'tür. Fakat siyahilerde ve kafkas ırkında daha erken yaşta ortaya çıkmaktadır (5). Hem DBBHL hem NHL'ların diğer alt gruplarında ailesel birliktelik bildirilmiştir (6).

PATOGENEZ

DBBHL patolojisi oldukça heterojendir, sentroblastik, immünoblastik, T-hücre ya da histiyositten zengin ve anaplastik subtipleri bulunmaktadır. Primer mediastinal B-hücreli lenfoma (PMBL), primer santral sinir sistemi lenfoması (PCNSL) gibi patolojik varyantıları da bulunmaktadır. Ayrıca DBBHL; KLL (Richter Sendromu), lenfoblastik lenfoma, foliküler lenfoma, marjinal zon lenfoma (MALT), splenik marjinal zon lenfoma gibi bazı düşük grade lenfomaların transformasyonu sonucu da oluşabilmektedir (7). Son zamanlarda, gen ekspresyonu profilinde saptanan gelişmeler ile morfolojik olarak fark göstermeyen tümörlerde belirgin gen ekspresyon heterojenitelerinin bulunduğu görülmüş, bu işaretlere göre B-hücre diferansiyasyonunun evresine göre DBBHL üç farklı subtipe ayrılmıştır; germinal center B-cell (GBC) benzeri, aktive B-cell (ABC) benzeri ve primer mediastinal B-cell lenfoma (PMBL). Standart tedavi ile bu subtiplerde elde edilen hayatta kalım süresi farklıdır. Özellikle ABC subtipinin daha kötü sağkalım ile ilişkili olduğu retrospektif çalışmalarda bildirilmektedir (8). DBBHL, AIDS ilişkili bir malignitedir. HIV ve EBV virüsünün NHL patogenezinde-

[1] Dr., Samsun Eğitim ve Araştırma Hastanesi, sudehatun@yahoo.com

REFERANSLAR

1. Morton LM, Wang SS, Devesa SS, Hartge P, Weisenburger DD, Linet MS. Lymphoma incidence patterns by WHO subtype in the United States, 1992-2001. Blood. 2006 Jan 1;107(1):265-76. PubMed PMID: 16150940. Pubmed Central PMCID: 1895348.
2. van Leeuwen MT, Turner JJ, Joske DJ, Falster MO, Srasuebkul P, Meagher NS, et al. Lymphoid neoplasm incidence by WHO subtype in Australia 1982-2006. International journal of cancer. 2014 Nov 1;135(9):2146-56. PubMed PMID: 24639369.
3. Smith A, Howell D, Patmore R, Jack A, Roman E. Incidence of haematological malignancy by sub-type: a report from the Haematological Malignancy Research Network. British journal of cancer. 2011 Nov 22;105(11):1684-92. PubMed PMID: 22045184. Pubmed Central PMCID: PMC3242607. Epub 2011/11/03. eng.
4. Sant M, Allemani C, Tereanu C, De Angelis R, Capocaccia R, Visser O, et al. Incidence of hematologic malignancies in Europe by morphologic subtype: results of the HAEMACARE project. Blood. 2010 Nov 11;116(19):3724-34. PubMed PMID: 20664057. Epub 2010/07/29. eng.
5. Shenoy PJ, Malik N, Nooka A, Sinha R, Ward KC, Brawley OW, et al. Racial differences in the presentation and outcomes of diffuse large B-cell lymphoma in the United States. Cancer. 2011 Jun 1;117(11):2530-40. PubMed PMID: 24048801. Epub 2011/06/01. eng.
6. Goldin LR, Landgren O, McMaster ML, Gridley G, Hemminki K, Li X, et al. Familial aggregation and heterogeneity of non-Hodgkin lymphoma in population-based samples. Cancer epidemiology, biomarkers & prevention : a publication of the American Association for Cancer Research, cosponsored by the American Society of Preventive Oncology. 2005 Oct;14(10):2402-6. PubMed PMID: 16214923. Epub 2005/10/11. eng.
7. Sehn LH, Gascoyne RD. Diffuse large B-cell lymphoma: optimizing outcome in the context of clinical and biologic heterogeneity. Blood. 2015 Jan 1;125(1):22-32. PubMed PMID: 25499448. Epub 2014/12/17. eng.
8. Lenz G, Wright G, Dave SS, Xiao W, Powell J, Zhao H, et al. Stromal gene signatures in large-B-cell lymphomas. The New England journal of medicine. 2008 Nov 27;359(22):2313-23. PubMed PMID: 19038878. Epub 2008/11/29. eng.
9. Howlett C, Snedecor SJ, Landsburg DJ, Svoboda J, Chong EA, Schuster SJ, et al. Front-line, dose-escalated immunochemotherapy is associated with a significant progression-free survival advantage in patients with double-hit lymphomas: a systematic review and meta-analysis. British journal of haematology. 2015 Aug;170(4):504-14. PubMed PMID: 25907897. Epub 2015/04/25. eng.
10. Oki Y, Noorani M, Lin P, Davis RE, Neelapu SS, Ma L, et al. Double hit lymphoma: the MD Anderson Cancer Center clinical experience. British journal of haematology. 2014 Sep;166(6):891-901. PubMed PMID: 24943107. Epub 2014/06/20. eng.
11. Petrich AM, Gandhi M, Jovanovic B, Castillo JJ, Rajguru S, Yang DT, et al. Impact of induction regimen and stem cell transplantation on outcomes in double-hit lymphoma: a multicenter retrospective analysis. Blood. 2014 Oct 9;124(15):2354-61. PubMed PMID: 25161267. Epub 2014/08/28. eng.
12. Cheson BD, Fisher RI, Barrington SF, Cavalli F, Schwartz LH, Zucca E, et al. Recommendations for initial evaluation, staging, and response assessment of Hodgkin and non-Hodgkin lymphoma: the Lugano classification. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 2014 Sep 20;32(27):3059-

68. PubMed PMID: 25113753. Pubmed Central PMCID: PMC4979083. Epub 2014/08/13. eng.
13. A predictive model for aggressive non-Hodgkin's lymphoma. The New England journal of medicine. 1993 Sep 30;329(14):987-94. PubMed PMID: 8141877. Epub 1993/09/30. eng.
14. Pfreundschuh M. How I treat elderly patients with diffuse large B-cell lymphoma. Blood. 2010 Dec 9;116(24):5103-10. PubMed PMID: 20805363. Epub 2010/09/02. eng.
15. Meguro A, Ozaki K, Sato K, Oh I, Fujiwara S, Hosonuma R, et al. Rituximab plus 70% cyclophosphamide, doxorubicin, vincristine and prednisone for Japanese patients with diffuse large B-cell lymphoma aged 70 years and older. Leukemia & lymphoma. 2012 Jan;53(1):43-9. PubMed PMID: 21864040. Epub 2011/08/26. eng.
16. Peyrade F, Jardin F, Thieblemont C, Thyss A, Emile JF, Castaigne S, et al. Attenuated immunochemotherapy regimen (R-miniCHOP) in elderly patients older than 80 years with diffuse large B-cell lymphoma: a multicentre, single-arm, phase 2 trial. The Lancet Oncology. 2011 May;12(5):460-8. PubMed PMID: 21482186. Epub 2011/04/13. eng.
17. Aviles A, Nambo MJ, Neri N, Cleto S, Castaneda C, Huerta-Guzman J, et al. Dose dense (CEOP-14) vs dose dense and rituximab (CEOP-14 +R) in high-risk diffuse large cell lymphoma. Medical oncology (Northwood, London, England). 2007;24(1):85-9. PubMed PMID: 17673816. Epub 2007/08/04. eng.
18. Chao NJ, Rosenberg SA, Horning SJ. CEPP(B): an effective and well-tolerated regimen in poor-risk, aggressive non-Hodgkin's lymphoma. Blood. 1990 Oct 1;76(7):1293-8. PubMed PMID: 2207307. Epub 1990/10/01. eng.
19. Gutierrez M, Chabner BA, Pearson D, Steinberg SM, Jaffe ES, Cheson BD, et al. Role of a doxorubicin-containing regimen in relapsed and resistant lymphomas: an 8-year follow-up study of EPOCH. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 2000 Nov 1;18(21):3633-42. PubMed PMID: 11054436. Epub 2000/10/31. eng.
20. Zhou Z, Sehn LH, Rademaker AW, Gordon LI, Lacasce AS, Crosby-Thompson A, et al. An enhanced International Prognostic Index (NCCN-IPI) for patients with diffuse large B-cell lymphoma treated in the rituximab era. Blood. 2014 Feb 6;123(6):837-42. PubMed PMID: 24264230. Pubmed Central PMCID: PMC5527396. Epub 2013/11/23. eng.
21. Spina M, Balzarotti M, Uziel L, Ferreri AJ, Fratino L, Magagnoli M, et al. Modulated chemotherapy according to modified comprehensive geriatric assessment in 100 consecutive elderly patients with diffuse large B-cell lymphoma. The oncologist. 2012;17(6):838-46. PubMed PMID: 22610154. Pubmed Central PMCID: PMC3380883. Epub 2012/05/23. eng.
22. Arnold S Freedman JWF. Initial treatment of limited stage diffuse large B cell lymphoma, . wwwuptodatecom ©2018 UpToDate. 2018.
23. Arnold S Freedman JWF. Initial treatment of advanced stage diffuse large B cell lymphoma. wwwuptodatecom ©2018 UpToDate. 2018.
24. Arnold S Freedman JWF. Treatment of relapsed or refractory diffuse large B cell lymphoma. wwwuptodatecom ©2018 UpToDate. 2018.
25. Schmitz N, Zeynalova S, Nickelsen M, Kansara R, Villa D, Sehn LH, et al. CNS International Prognostic Index: A Risk Model for CNS Relapse in Patients With Diffuse Large B-Cell Lymphoma Treated With R-CHOP. Journal of clinical oncology : offici-

al journal of the American Society of Clinical Oncology. 2016 Sep 10;34(26):3150-6. PubMed PMID: 27382100. Epub 2016/07/07. eng.

26. Vitolo U, Chiappella A, Ferreri AJ, Martelli M, Baldi I, Balzarotti M, et al. First-line treatment for primary testicular diffuse large B-cell lymphoma with rituximab-CHOP, CNS prophylaxis, and contralateral testis irradiation: final results of an international phase II trial. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 2011 Jul 10;29(20):2766-72. PubMed PMID: 21646602. Epub 2011/06/08. eng.
27. Bernstein SH, Unger JM, Leblanc M, Friedberg J, Miller TP, Fisher RI. Natural history of CNS relapse in patients with aggressive non-Hodgkin's lymphoma: a 20-year follow-up analysis of SWOG 8516 -- the Southwest Oncology Group. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 2009 Jan 1;27(1):114-9. PubMed PMID: 19047289. Pubmed Central PMCID: PMC4879698. Epub 2008/12/03. eng.
28. Ferreri AJ, Guerra E, Regazzi M, Pasini F, Ambrosetti A, Pivnik A, et al. Area under the curve of methotrexate and creatinine clearance are outcome-determining factors in primary CNS lymphomas. British journal of cancer. 2004 Jan 26;90(2):353-8. PubMed PMID: 14735176. Pubmed Central PMCID: PMC2409565. Epub 2004/01/22. eng.
29. McMillan A, Ardeshna KM, Cwynarski K, Lyttelton M, McKay P, Montoto S. Guideline on the prevention of secondary central nervous system lymphoma: British Committee for Standards in Haematology. British journal of haematology. 2013 Oct;163(2):168-81. PubMed PMID: 24033102. Epub 2013/09/17. eng.
30. Liang R, Chiu E, Loke SL. Secondary central nervous system involvement by non-Hodgkin's lymphoma: the risk factors. Hematological oncology. 1990 May-Jun;8(3):141-5. PubMed PMID: 2373491. Epub 1990/05/01. eng.
31. Friedberg JW, Sharman J, Sweetenham J, Johnston PB, Vose JM, Lacasce A, et al. Inhibition of Syk with fostamatinib disodium has significant clinical activity in non-Hodgkin lymphoma and chronic lymphocytic leukemia. Blood. 2010 Apr 1;115(13):2578-85. PubMed PMID: 19965662. Pubmed Central PMCID: PMC2852362. Epub 2009/12/08. eng.
32. Wilson WH, Young RM, Schmitz R, Yang Y, Pittaluga S, Wright G, et al. Targeting B cell receptor signaling with ibrutinib in diffuse large B cell lymphoma. Nature medicine. 2015 Aug;21(8):922-6. PubMed PMID: 26193343. Epub 2015/07/21. eng.
33. Byrd JC, Harrington B, O'Brien S, Jones JA, Schuh A, Devereux S, et al. Acalabrutinib (ACP-196) in Relapsed Chronic Lymphocytic Leukemia. The New England journal of medicine. 2016 Jan 28;374(4):323-32. PubMed PMID: 26641137. Pubmed Central PMCID: PMC4862586. Epub 2015/12/08. eng.
34. Wilson WH, O'Connor OA, Czuczman MS, LaCasce AS, Gerecitano JF, Leonard JP, et al. Navitoclax, a targeted high-affinity inhibitor of BCL-2, in lymphoid malignancies: a phase 1 dose-escalation study of safety, pharmacokinetics, pharmacodynamics, and antitumour activity. The Lancet Oncology. 2010 Dec;11(12):1149-59. PubMed PMID: 21094089. Pubmed Central PMCID: PMC3025495. Epub 2010/11/26. eng.
35. Phase I study of ABT-199 (GDC-0199) in patients with relapsed/refractory non-Hodgkin lymphoma: responses observed in diffuse large B-cell (DLBCL) and follicular lymphoma (FL) at higher cohort doses. Clinical advances in hematology & oncology : H&O. 2014 Aug;12(8 Suppl 16):18-9. PubMed PMID: 25768998. Epub 2015/03/15. eng.

36. Morin RD, Johnson NA, Severson TM, Mungall AJ, An J, Goya R, et al. Somatic mutations altering EZH2 (Tyr641) in follicular and diffuse large B-cell lymphomas of germinal-center origin. Nature genetics. 2010 Feb;42(2):181-5. PubMed PMID: 20081860. Pubmed Central PMCID: PMC2850970. Epub 2010/01/19. eng.
37. Italiano A, Soria JC, Toulmonde M, Michot JM, Lucchesi C, Varga A, et al. Tazemetostat, an EZH2 inhibitor, in relapsed or refractory B-cell non-Hodgkin lymphoma and advanced solid tumours: a first-in-human, open-label, phase 1 study. The Lancet Oncology. 2018 May;19(5):649-59. PubMed PMID: 29650362. Epub 2018/04/14. eng.
38. Ansell SM, Hurvitz SA, Koenig PA, LaPlant BR, Kabat BF, Fernando D, et al. Phase I study of ipilimumab, an anti-CTLA-4 monoclonal antibody, in patients with relapsed and refractory B-cell non-Hodgkin lymphoma. Clinical cancer research : an official journal of the American Association for Cancer Research. 2009 Oct 15;15(20):6446-53. PubMed PMID: 19808874. Pubmed Central PMCID: PMC2763019. Epub 2009/10/08. eng.
39. Ansell SM, Lesokhin AM, Borrello I, Halwani A, Scott EC, Gutierrez M, et al. PD-1 blockade with nivolumab in relapsed or refractory Hodgkin's lymphoma. The New England journal of medicine. 2015 Jan 22;372(4):311-9. PubMed PMID: 25482239. Pubmed Central PMCID: PMC4348009. Epub 2014/12/09. eng.
40. Sadelain M. CAR therapy: the CD19 paradigm. The Journal of clinical investigation. 2015 Sep;125(9):3392-400.