·综述·

弥漫大B细胞淋巴瘤临床预后系统与分子预后因素的研究进展

王书楠　白鸥

The advances of clinical and molecular prognostic factors of diffuse large B-cell lymphoma　*Wang Shu'nan, Bai Ou*

Corresponding author: Bai Ou, Cancer Center, The First Hospital of Jilin University, Changchun 130021, China. Email: oubai16@163.com

弥漫大B细胞淋巴瘤(diffuse large B-cell lymphoma, DLBCL)是非霍奇金淋巴瘤(NHL)中最常见的亚型,占西方成人NHL患者的30%~40%[1],占中国NHL患者的37.94%[2]。DLBCL在病理及临床方面呈高度异质性,患者对治疗的反应及预后也相差很大。分子病理及靶向治疗的发展,使DLBCL的预后评估因素有了很大进展。临床预后评估系统由国际预后指数(IPI),逐渐进展为年龄调整的IPI(aa-IPI)、改良的IPI(R-IPI)、NCCN-IPI,而且出现了新的分子预后因素,主要包括生发中心/非生发中心(GCB/non-GCB)分子亚型、Ki-67、C-Myc、Bcl-2、CD5、p53等。在本文中我们将就DLBCL临床预后系统的演进及分子预后因素的研究进展进行综述。

一、临床预后评估系统

IPI是目前应用最广泛的预后评估系统[3],包括年龄、体能状态、LDH、临床分期、结外器官受累数目5个因素,将DLBCL分为4个危险组。之后发现年龄是极为重要的预后因素,于是特别针对年龄<60岁的患者,形成aa-IPI[3]。在单纯化疗时代,IPI对于DLBCL的预后评估起很大作用。伴随CD20单克隆抗体的应用,DLBCL的治疗进入免疫化疗时代。Sehn等[4]研究显示IPI不能很好地评估R-CHOP方案治疗患者的预后,因此制定了R-IPI,将R-CHOP方案治疗的患者分为低危、中危、高危3个危险组,克服了之前低危与低中危组、中高危与高危组患者间生存曲线相互融合的问题。2014年Zhou等[5]通过对NCCN数据库资料进行分析,进一步针对IPI预后因素中的年龄、LDH进行细化,形成NCCN-IPI评估系统。与IPI相比,它适合所有方案治疗的患者,且患者均可以很好地分为低危、低中危、中高危及高危组。Melchardt等[6]对499例DLBCL患者进行分析,发现增加血浆白蛋白指标,可以使低危组的界限更精准,改善对老年DLBCL患者的预后分层,从而形成了改良的NCCN-IPI。

经历20年的进展,DLBCL的预后评估系统已经由来源于单纯化疗时期的IPI演进为更加细化、准确的NCCN-IPI,使DLBCL的预后评估更加完善,增加了个体化治疗的科学依据。然而随着分子预后新指标的不断出现,临床评估系统的预后作用已逐渐减弱,需要引起更多的关注。

二、分子预后因素

依据基因表达谱(GEP),DLBCL分为GCB、活化B细胞样(ABC)、UNC(不能分类型)3个不同的分子亚型。依据免疫组化Hans/Tally/Choi模型,分为GCB和non-GCB亚型。研究表明,不论是CHOP/CHOP样方案;还是R-CHOP方案,non-GCB亚型都是DLBCL独立的不良预后因素。Lenz等[7]对233例DLBCL患者进行GEP检测确定分子亚型,给予R-CHOP方案治疗,GCB亚型者5年总生存(OS)率≥80%,ABC亚型者≤50%。分子亚型和IPI都是DLBCL患者独立的预后因素,但是目前还没有一个系统将二者结合起来进行预后评估。随着分子病理学的进展,新的分子预后指标不断出现,目前具有独立预后意义的分子预后因素主要包括Ki-67、C-Myc、Bcl-2、CD5、p53等。

1. Ki-67:Ki-67为细胞核抗原,是细胞增殖标志物,也是恶性肿瘤重要的预后指标。Gaudio等[8]对接受CHOP/R-CHOP方案治疗的111例初诊DLBCL患者进行研究发现,接受R-CHOP方案治疗患者的Ki-67高表达(>80%)是患者OS、无进展生存(PFS)率降低的独立危险因素。但也有研究者认为,Ki-67高表达与DLBCL患者的预后无关[9]。最近有研究者对580例接受R-CHOP方案治疗的初诊DLBCL患者进行研究,发现Ki-67高表达(>70%)是影响伴有骨髓浸润者OS和PFS的独立预后因素(P值均<0.001)[10]。综上,多数研究者认为Ki-67高表达是DLBCL独立预后因素。但由于检测标准的差异,高表达的界定存在偏差,可能导致对预后的判定意义有所不同。

2. C-Myc:C-Myc是存在于8q24的原癌基因,编码的蛋白属于核转录调控因子,控制>10%的人类基因组基因。C-Myc基因和蛋白表达异常,与细胞增殖、分化和凋亡密切相关。有5%~10%的DLBCL患者存在C-Myc基因重排,该类患者对CHOP/CHOP样、R-CHOP方案或增强方案的疗效均很差。Zhou等[11]首次通过meta研究证实,C-Myc基因对DLBCL患者具有预后价值,C-Myc基因和蛋白表达异常者较不伴有者的OS和无事件生存(EFS)期短(基因异常:OS:HR=2.22, 95% CI 1.89~2.61; EFS: HR=2.29, 95% CI 1.81~

DOI:10.3760/cma.j.issn.0253-2727.2016.06.022

基金项目:吉林省省级经济结构战略调整引导资金专项(2014Y090)

作者单位:130021　长春,吉林大学第一医院肿瘤中心

通信作者:白鸥,Email:oubai16@163.com

2.90。蛋白异常：OS：*HR*=2.13，95% *CI* 1.55~2.91；EFS：*HR*=2.21，95% *CI* 1.36~3.61）。Yoon等[12]研究证实，C-Myc异常以GCB亚型多见。

3. Bcl-2：Bcl-2是凋亡抑制基因，阳性表达诱导淋巴瘤细胞产生耐药。30%~60%的DLBCL患者高表达Bcl-2，在单纯化疗时代是独立于IPI的预后因素[13]。Mounier等[14]研究发现，在Bcl-2阳性的DLBCL患者中，R-CHOP方案治疗组的总有效率及PFS、OS率显著高于CHOP方案治疗组；Bcl-2阴性患者中则两组治疗方案上述差异无统计学意义，提示利妥昔单抗可克服Bcl-2带来的不利预后。

4. CD5：CD5是跨膜糖蛋白，主要表达于正常T细胞，少部分表达于正常或恶变的B细胞。5%~10%的DLBCL患者伴有CD5阳性，临床特征为老年女性较多、结外浸润、初诊为晚期、预后很差，R-CHOP方案可改善其PFS率，但不能改善OS率[15]。Miyazaki等[16]研究发现，12%的CD5阳性DLBCL患者伴有中枢神经系统累及，OS率较阴性者明显降低（*P*<0.001）。CD5阳性DLBCL以non-GCB型为主[15,17]。

5. p53：p53是重要的抑癌基因。有研究显示，21.4%的DLBCL患者伴有p53基因突变，其中90.2%为单一核苷酸突变，9.8%为其他突变；p53基因突变主要影响GCB亚型患者的预后[18]。Kaplan-Meier分析结果显示，p53基因突变患者的预后明显差于无突变者，是DLBCL患者的独立预后因素[19-20]。

与治疗相关的最新分子预后进展详见表1。DLBCL相关信号通路有BCR信号途径、NF-κB信号途径、JAK-STAT信号途径等，与其相关的特异性抑制剂正不断出现[21-38]。其中硼替佐米、Ibrutinib可以抑制NF-κB的活性，在治疗复发难治性ABC型DLBCL患者方面获得广泛关注[39]。最新研究表明，Ibrutinib与S-Mepazin可以协同作用治疗CD79突变的DLBCL[40]，与HSp90信号通路相关的elF4E抑制剂可与HSp70抑制剂协同作用从而发挥对双打击或三打击DLBCL的抗肿瘤活性[41]，Cerdulatinib对ABC型和GCB型DLBCL患者均有显著的治疗效果[24]。可见靶向药物不仅在单独使用时疗效好，部分还可以协同作用增强疗效，也有靶向药物在不同信号通路均有作用靶点因而治疗效果显著，因此靶向治疗有望明显改善DLBCL患者的预后。

总之，non-GCB亚型、Ki-67高表达、C-Myc及Bcl-2基因异常、CD5阳性表达的DLBCL患者预后差，这些分子预后标志在临床预后评估系统的基础上进一步将DLBCL患者的预后分为不同亚层。随着对DLBCL相关信号通路研究的不断深入，与其相关的特异性抑制剂也不断出现，部分药物经临床试验证实具有显著的治疗效果，对于改善患者预后有重要意义。随着精准医学时代的到来，是否可以将临床与分子预后因素相结合，建立更加完善的DLBCL预后评估体系，同时充分应用靶向治疗的优势，从而实施更加精准的个体化治疗，依然需要全球性、多中心、大样本的临床研究。

参考文献

[1] Martelli M, Ferreri AJ, Agostinelli C, et al. Diffuse large B-cell lymphoma[J]. Crit Rev Oncol Hematol, 2013, 87(2): 146-171. doi: 10.1016/j.critrevonc.2012.12.009.

[2] 李小秋, 李甘地, 高子芬, 等. 中国淋巴瘤亚型分布:国内多中心性病例10002例分析[J]. 诊断学理论与实践, 2012, 11(2): 111-115. doi: 10.3969/j.issn.1671-2870.2012.02.006.

[3] A predictive model for aggressive non-Hodgkin's lymphoma. The International Non- Hodgkin's Lymphoma Prognostic Factors Project[J]. N Engl J Med, 1993, 329(14): 987-994. doi: 10.1056/NEJM199309303291402.

[4] Sehn LH, Berry B, Chhanabhai M, et al. The revised International Prognostic Index (R- IPI) is a better predictor of outcome than the standard IPI for patients with diffuse large B- cell lymphoma treated with R- CHOP[J]. Blood, 2007, 109(5): 1857-1861. doi: 10.1182/blood-2006-08-038257.

表1 DLBCL相关信号通路及靶向药物

信号通路	作用靶点	药物名称	作者及参考文献
BCR信号途径	Syk	FosD（R788）、GS9973、Cerdulatinib、R406	Suljagic等[22]，Sharman等[23]，Ma等[24]，Szydlowski等[25]
	BTK	Ibrutinib（PCI-32765）、QL-X-138	Herman等[26]，Wu等[27]
NF-κB信号途径	MALT1	Z-VRPR-FMK、S-Mepazin Phenothiazine衍生物（Mepazine、Thioridozine Promazine）	Nagel等[28]
	IKK	Withaferin A、JQ1	Jackson等[29]，Ceribelli等[30]
	IκB	Bay 11-7085	Hussain等[31]
	PI3K	Idelalisib（GS-1101或CAL-101）	Bodo等[32]
PI3K/Akt/mTOR信号途径	Akt	Perifosine、MK-2206、Nelfinavir	Friedman等[33]，Petrich等[34]
	mTOR	Temsirolimus、Everoliums（RAD001）	Hess等[35]，Barnes等[36]
JAK-STAT信号途径	JAK	Pacritinib（SB-1518）、Cerdulatinib	Derenzini等[37]，Ma等[24]
Raf-MEK-ERK信号途径	MNK	Cercosporamide、QL-X-138	Sussman等[38]，Wu等[27]

注：BCR：B细胞受体；Syk：脾酪氨酸激酶；BTK：布鲁顿酪氨酸激酶；MALT1：黏膜相关淋巴组织蛋白1；IKK：人κB抑制蛋白激酶；IκB：核因子κB的抑制蛋白；PI3K：磷脂酰肌醇3-激酶；Akt：丝氨酸/苏氨酸蛋白激酶；mTOR：哺乳动物雷帕霉素靶蛋白；JAK：Janus激酶；MNK：丝裂原活化蛋白激酶作用激酶

[5] Zhou Z, Sehn LH, Rademaker AW, et al. An enhanced International Prognostic Index (NCCN-IPI) for patients with diffuse large B-cell lymphoma treated in the rituximab era[J]. Blood, 2014, 123(6): 837-842. doi: 10.1182/blood-2013-09-524108.

[6] Melchardt T, Troppan K, Weiss L, et al. A modified scoring of the NCCN-IPI is more accurate in the elderly and is improved by albumin and β2 -microglobulin[J]. Br J Haematol, 2015, 168(2): 239-245. doi: 10.1111/bjh.13116.

[7] Lenz G, Wright G, Dave SS, et al. Stromal gene signatures in large-B-cell lymphomas[J]. N Engl J Med, 2008, 359(22): 2313-2323. doi: 10.1056/NEJMoa0802885.

[8] Gaudio F, Giordano A, Perrone T, et al. High Ki67 index and bulky disease remain significant adverse prognostic factors in patients with diffuse large B cell lymphoma before and after the introduction of rituximab[J]. Acta Haematol, 2011, 126(1): 44-51. doi: 10.1159/000324206.

[9] Yan LX, Liu YH, Luo DL, et al. MYC expression in concert with BCL2 and BCL6 expression predicts outcome in Chinese patients with diffuse large B-cell lymphoma, not otherwise specified[J]. PLoS One, 2014, 9(8): e104068. doi: 10.1371/journal.pone.0104068.

[10] Song MK, Chung JS, Lee JJ, et al. High Ki-67 expression in involved bone marrow predicts worse clinical outcome in diffuse large B cell lymphoma patients treated with R-CHOP therapy[J]. Int J Hematol, 2015, 101(2): 140-147. doi: 10.1007/s12185-014-1719-3.

[11] Zhou K, Xu D, Cao Y, et al. C-MYC aberrations as prognostic factors in diffuse large B-cell lymphoma: a meta-analysis of epidemiological studies[J]. PLoS One, 2014, 9(4): e95020. doi: 10.1371/journal.pone. 0095020.

[12] Yoon SO, Jeon YK, Paik JH, et al. MYC translocation and an increased copy number predict poor prognosis in adult diffuse large B-cell lymphoma (DLBCL), especially in germinal centre-like B cell (GCB) type[J]. Histopathology, 2008, 53(2): 205-217. doi: 10.1111/j.1365-2559.2008.03076.x.

[13] Martinka M, Comeau T, Foyle A, et al. Prognostic significance of t(14;18) and bcl-2 gene expression in follicular small cleaved cell lymphoma and diffuse large cell lymphoma[J]. Clin Invest Med, 1997, 20(6): 364-370.

[14] Mounier N, Briere J, Gisselbrecht C, et al. Rituximab plus CHOP (R-CHOP) overcomes bcl-2-- associated resistance to chemotherapy in elderly patients with diffuse large B-cell lymphoma (DLBCL)[J]. Blood, 2003, 101(11): 4279-4284. doi: 10.1182/blood-2002-11-3442.

[15] Niitsu N, Okamoto M, Tamaru JI, et al. Clinicopathologic characteristics and treatment outcome of the addition of rituximab to chemotherapy for CD5-positive in comparison with CD5-negative diffuse large B-cell lymphoma[J]. Ann Oncol, 2010, 21(10): 2069-2074. doi: 10.1093/annonc/mdq057.

[16] Miyazaki K, Yamaguchi M, Suzuki R, et al. CD5-positive diffuse large B-cell lymphoma: a retrospective study in 337 patients treated by chemotherapy with or without rituximab[J]. Ann Oncol, 2011, 22(7): 1601-1607. doi: 10.1093/annonc/mdq627.

[17] Alizadeh AA, Eisen MB, Davis RE, et al. Distinct types of diffuse large B-cell lymphoma identified by gene expression profiling[J]. Nature, 2000, 403(6769): 503-511. doi: 10.1038/35000501.

[18] Young KH, Leroy K, Møller MB, et al. Structural profiles of TP53 gene mutations predict clinical outcome in diffuse large B-cell lymphoma: an international collaborative study[J]. Blood, 2008, 112(8): 3088-3098. doi: 10.1182/blood-2008-01-129783.

[19] Zhou M, Cen L, Chen T, et al. The Prognostic Significance of the Serum p53 Protein Concentration in Chinese Patients with Non-Hodgkin Lymphoma[J]. Turk J Haematol, 2012, 29(4): 376-384. doi: 10.5505/tjh.2012. 57338.

[20] Xu-Monette ZY, Wu L, Visco C, et al. Mutational profile and prognostic significance of TP53 in diffuse large B-cell lymphoma patients treated with R-CHOP: report from an International DLBCL Rituximab-C HOP Consortium Program Study[J]. Blood, 2012, 120(19): 3986-3996. doi: 10.1182/blood-2012-05-433334.

[21] 江传和, 王健民. B细胞非霍奇金淋巴瘤中信号通路抑制剂的研究进展[J].中华血液学杂志, 2015, 36(12): 1049-1052. doi: 10.3760/cma.j.issn.0253-2727.2015.12.015.

[22] Suljagic M, Longo PG, Bennardo S, et al. The Syk inhibitor fostamatinib disodium (R788) inhibits tumor growth in the Eμ-TCL1 transgenic mouse model of CLL by blocking antigen-dependent B-cell receptor signaling[J]. Blood, 2010, 116(23): 4894-4905. doi: 10.1182/blood-2010-03-275180.

[23] Sharman J, Hawkins M, Kolibaba K, et al. An open-label phase 2 trial of entospletinib (GS-9973), a selective spleen tyrosine kinase inhibitor, in chronic lymphocytic leukemia[J]. Blood, 2015, 125(15): 2336-2343. doi: 10.1182/blood-2014-08-595934.

[24] Ma J, Xing W, Coffey G, et al. Cerdulatinib, a novel dual SYK/JAK kinase inhibitor, has broad anti-tumor activity in both ABC and GCB types of diffuse large B cell lymphoma[J]. Oncotarget, 2015, 6(41): 43881-43896. doi: 10.18632/oncotarget.6316.

[25] Szydlowski M, Kiliszek P, Sewastianik T, et al. FOXO1 activation is an effector of SYK and AKT inhibition in tonic BCR signal-dependent diffuse large B-cell lymphomas[J]. Blood, 2016, 127(6): 739-748. doi: 10.1182/blood-2015-06-654111.

[26] Herman SE, Gordon AL, Hertlein E, et al. Bruton tyrosine kinase represents a promising therapeutic target for treatment of chronic lymphocytic leukemia and is effectively targeted by PCI-32765[J]. Blood, 2011, 117(23): 6287-6296. doi: 10.1182/blood-2011-01-328484.

[27] Wu H, Hu C, Wang A, et al. Discovery of a BTK/MNK dual inhibitor for lymphoma and leukemia[J]. Leukemia, 2016, 30(1): 173-181.doi: 10.1038/leu.2015.180.

[28] Nagel D, Spranger S, Vincendeau M, et al. Pharmacologic inhibition of MALT1 protease by phenothiazines as a

therapeutic approach for the treatment of aggressive ABC-DLBCL[J]. Cancer Cell, 2012, 22(6): 825-837. doi: 10.1016/j.ccr.2012.11.002.

[29] Jackson SS, Oberley C, Hooper CP, et al. Withaferin A disrupts ubiquitin-based NEMO reorganization induced by canonical NF-κB signaling[J]. Exp Cell Res, 2015, 331(1): 58-72. doi: 10.1016/j.yexcr.2014.09.034.

[30] Ceribelli M, Kelly PN, Shaffer AL, et al. Blockade of oncogenic IκB kinase activity in diffuse large B-cell lymphoma by bromodomain and extraterminal domain protein inhibitors[J]. Proc Natl Acad Sci U S A, 2014, 111(31): 11365-11370. doi: 10.1073/pnas.1411701111.

[31] Hussain AR, Ahmed SO, Ahmed M, et al. Cross-talk between NFkB and the PI3-kinase/AKT pathway can be targeted in primary effusion lymphoma (PEL) cell lines for efficient apoptosis[J]. PLoS One, 2012, 7(6): e39945. doi: 10.1371/journal.pone.0039945.

[32] Bodo J, Zhao X, Sharma A, et al. The phosphatidylinositol 3-kinases (PI3K) inhibitor GS-1101 synergistically potentiates histone deacetylase inhibitor-induced proliferation inhibition and apoptosis through the inactivation of PI3K and extracellular signal-regulated kinase pathways[J]. Br J Haematol, 2013, 163(1): 72-80. doi: 10.1111/bjh.12498.

[33] Friedman DR, Lanasa MC, Davis PH, et al. Perifosine treatment in chronic lymphocytic leukemia: results of a phase II clinical trial and in vitro studies[J]. Leuk Lymphoma, 2014, 55(5): 1067-1075. doi: 10.3109/10428194.2013.824080.

[34] Petrich AM, Leshchenko V, Kuo PY, et al. Akt inhibitors MK-2206 and nelfinavir overcome mTOR inhibitor resistance in diffuse large B-cell lymphoma[J]. Clin Cancer Res, 2012, 18(9): 2534-2544. doi: 10.1158/1078-0432.CCR-11-1407.

[35] Hess G, Herbrecht R, Romaguera J, et al. Phase III study to evaluate temsirolimus compared with investigator's choice therapy for the treatment of relapsed or refractory mantle cell lymphoma[J]. J Clin Oncol, 2009, 27(23): 3822-3829. doi: 10.1200/JCO.2008.20.7977.

[36] Barnes JA, Jacobsen E, Feng Y, et al. Everolimus in combination with rituximab induces complete responses in heavily pretreated diffuse large B-cell lymphoma[J]. Haematologica, 2013, 98(4): 615-619. doi: 10.3324/haematol.2012.075184.

[37] Derenzini E, Younes A. Targeting the JAK-STAT pathway in lymphoma: a focus on pacritinib[J]. Expert Opin Investig Drugs, 2013, 22(6): 775-785. doi: 10.1517/13543784.2013.775244.

[38] Sussman A, Huss K, Chio LC, et al. Discovery of cercosporamide, a known antifungal natural product, as a selective Pkc1 kinase inhibitor through high-throughput screening[J]. Eukaryot Cell, 2004, 3(4): 932-943. doi: 10.1128/EC.3.4.932-943.2004.

[39] Dasmahapatra G, Patel H, Dent P, et al. The Bruton tyrosine kinase (BTK) inhibitor PCI-32765 synergistically increases proteasome inhibitor activity in diffuse large-B cell lymphoma (DLBCL) and mantle cell lymphoma (MCL) cells sensitive or resistant to bortezomib[J]. Br J Haematol, 2013, 161(1): 43-56. doi: 10.1111/bjh.12206.

[40] Nagel D, Bognar M, Eitelhuber AC, et al. Combinatorial BTK and MALT1 inhibition augments killing of CD79 mutant diffuse large B cell lymphoma[J]. Oncotarget, 2015, 6(39): 42232-42242. doi: 10.18632/oncotarget. 6273.

[41] Culjkovic-Kraljacic B, Fernando TM, Marullo R, et al. Combinatorial targeting of nuclear export and translation of RNA inhibits aggressive B-cell lymphomas[J]. Blood, 2016, 127(7): 858-868. doi: 10.1182/blood-2015-05-645069.

(收稿日期:2015-12-05)

(本文编辑:刘志红)

本刊编辑部人员联系方式

董文革:022-23909100,Email:dongwenge@ihcams.ac.cn
刘志红:022-23909350,Email:liuzhihong@ihcams.ac.cn
徐茂强:022-23909421,Email:xumaoqiang@ihcams.ac.cn
李梅:022-23909350,Email:limei@ihcams.ac.cn
王叶青:022-23909421,Email:wangyeqing@ihcams.ac.cn
刘爽:022-23909430,Email:liushuang@ihcams.ac.cn
编辑部:022-27304167,Email:zhxyx@hematoline.com
本刊网址:http://www.hematoline.com