·综　述·

# 非特指EBV阳性弥漫大B细胞淋巴瘤的研究进展

陈光亮，吴方恬，曹军宁

复旦大学附属肿瘤医院淋巴瘤科，复旦大学上海医学院肿瘤学系，上海 200032

［**摘要**］ EB病毒（Epstein-Barr virus，EBV）感染人体后，可长期潜伏于静息记忆性或幼稚B淋巴细胞中。随着免疫系统的衰老，EBV感染者发生EBV相关恶性肿瘤的风险明显增加。非特指EBV阳性弥漫大B细胞淋巴瘤（EBV positive diffuse large B-cell lymphoma, not otherwise specified，EBV$^+$DLBCL-NOS）是指发生在无已知免疫缺陷疾病或淋巴瘤病史，且肿瘤细胞核表达EBV编码RNA（EBV encoded RNA，EBER）的大B细胞淋巴瘤。流行病学研究显示，EBV$^+$DLBCL-NOS主要流行于亚洲及拉丁美洲，多数患者年龄超过50岁。临床上，与EBV阴性DLBCL（EBV negative DLBCL，EBV$^-$DLBCL）患者相比，EBV$^+$DLBCL-NOS患者的临床病程更具侵袭性，初诊患者的临床分期多为晚期，且结外受累率可超过80%。老年患者通常较年轻患者的预后更差。尽管包括利妥昔单抗的免疫化疗方案可显著提高EBV$^-$DLBCL患者的预后，EBV$^+$DLBCL-NOS的最佳一线治疗方案仍需进一步探索。由于EBV$^+$DLBCL-NOS的发病率相对较低并存在地区分布的差异，也缺乏多中心、高质量的前瞻性临床研究，因此临床医师对该特殊亚型淋巴瘤的认知仍比较有限。随着二代测序等新技术的开展，发现EBV$^+$DLBCL-NOS的肿瘤细胞存在核因子-κB（nuclear factor-κB，NF-κB）和Janus激酶/信号转导和转录激活因子（Janus kinase/signal transducer and activator of transcription，JAK/STAT）等信号转导通路的改变，以及免疫过程如干扰素应答、抗原递呈系统和免疫检查点分子的异常等。这些基础研究成果促进了对相关治疗靶点的识别，有助于新治疗策略的探索。未来，嵌合抗原受体T细胞（chimeric antigen receptor T-cell，CAR-T）疗法、化疗联合免疫治疗及新型靶向治疗药物均有望改善EBV$^+$DLBCL-NOS患者的预后，但仍需要更多研究证实。

［**关键词**］ EB病毒；非霍奇金淋巴瘤；弥漫大B细胞淋巴瘤；免疫治疗；靶向治疗

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**Advances in research on EBV positive diffuse large B-cell lymphoma, not otherwise specified**

CHEN Guangliang, WU Fangtian, CAO Junning (Department of Lymphoma, Fudan University Shanghai Cancer Center; Department of Oncology, Shanghai Medical College, Fudan University, Shanghai 200032, China)

Correspondence to: CAO Junning E-mail: cao_junning@126.com

［**Abstract**］ Epstein-Barr virus (EBV) can be latent in resting memory or naive B lymphocytes for a long time in affected people. Aging-induced immunosenescence is associated with an increased risk of EBV−related malignancies in EBV−infected patients. EBV positive diffuse large B-cell lymphoma, not otherwise specified (EBV$^+$DLBCL-NOS) is identified as occurring in large B-cell lymphoma with no known history of immunodeficiency disease or lymphoma and whose tumor nuclei expressed EBV encoded RNA (EBER). The prevalence of EBV$^+$DLBCL-NOS is significantly higher in Asia and Latin America than in other regions worldwide, and it mainly affects patients aged 50 years or older. EBV$^+$DLBCL-NOS patients are associated with a more aggressive clinical course, a more advanced disease, and a higher rate of extra-nodal involvement (more than 80%) compared with EBV negative DLBCL (EBV$^-$DLBCL) patients. The elderly patients with EBV$^+$DLBCL-NOS have poorer overall survival and progression-free survival than young adults. Rituximab-containing immunochemotherapy significantly improves the prognosis of patients with EBV$^-$DLBCL, however, the optimal first-line treatment for EBV$^+$DLBCL-NOS still needs to be further explored. The current understanding of EBV$^+$DLBCL-NOS, a rare subtype of DLBCL, is very limited because of the relatively low incidence of EBV$^+$DLBCL-NOS with a regional difference, as well as lacking high-quality clinical study. However, the DLBCL field is changing rapidly with new technologies, such as next-generation sequencing. To date, few studies have reported that multiple cells signaling pathways are aberrantly activated in tumor cells of EBV$^+$DLBCL-NOS, such as nuclear factor-κB (NF-κB) and Janus kinase/signal transducer and activator of transcription (JAK/STAT). In addition, abnormalities in immune processes have been observed in tumor

通信作者：曹军宁　E-mail: cao_junning@126.com

cells of EBV$^+$DLBCL-NOS, such as the response to interferon, the antigen presentation system, and immune checkpoint molecules. The discovery of these basic research findings fosters the identification of relevant therapeutic targets and facilitates the exploration of novel therapeutic strategies. In the future, the benefits of immunotherapy, targeted therapy, and chimeric antigen receptor T-cell (CAR-T) therapy for EBV$^+$DLBCL-NOS patients remain unknown and require extensive research.

［**Key words**］ Epstein-Barr virus; Non-Hodgkin's lymphoma; Diffuse large B-cell lymphoma; Immunotherapy; Targeted therapy

EB病毒（Epstein-Barr virus，EBV）属于γ疱疹病毒亚科[1]，其规范名称是人类疱疹病毒4型（human herpesvirus 4，HHV-4），在1964年由Epstein研究小组从一种伯基特淋巴瘤的细胞系中分离出来，也是第一种被证实与人类癌症发病密切相关的双链DNA病毒[2-3]。EBV主要通过唾液传播[4]，普通人群隐匿感染率高达90%[1-3]。多项研究[5-6]表明，EBV感染幼稚B淋巴细胞主要依赖于CD21，在一定条件下，可促使B淋巴细胞增殖和恶变。抗原特异性T淋巴细胞可清除EBV感染的B淋巴细胞，而EBV潜伏于不表达病毒蛋白抗原的静息记忆B细胞中则可逃避免疫系统的监视，成为隐匿性EBV感染者[2-3]。随着年龄增长和免疫系统的衰老，特别是T淋巴细胞免疫功能下降，EBV隐匿感染者罹患EBV相关恶性肿瘤的风险显著增加[2-3，7]，包括伯基特淋巴瘤、免疫缺陷相关性非霍奇金淋巴瘤（non-Hodgkin's lymphoma，NHL）、结外自然杀伤/T细胞淋巴瘤（natural killer/T-cell lymphoma，NK/TL）、霍奇金淋巴瘤、鼻咽癌和胃癌等。

弥漫大B细胞淋巴瘤（diffuse large B-cell lymphoma，DLBCL）是最常见的恶性B细胞性淋巴瘤[1，8-10]，占NHL的33.3%~36.2%[10-11]。DLBCL的病因和发病机制十分复杂，最近的分子分型研究[9]提示，DLBCL的疾病谱具有高度异质性。目前认为，EBV感染在EBV阳性DLBCL（EBV positive DLBCL，EBV$^+$DLBCL）患者的疾病发生过程中发挥重要作用[7，9，12]。

## 1 EBV$^+$DLBCL的定义和分类演变过程

2003年，Oyama等[13]最早报道了22例肿瘤细胞核EBV$^+$的老年DLBCL患者，发现这些患者与免疫缺陷性EBV相关淋巴细胞增殖性疾病（lymphoproliferative disorders，LPD）患者具有类似的临床特征。2007年，Ok等[14]进一步总结了96例患者的临床病理学资料，发现与EBV阴性DLBCL（EBV negative DLBCL，EBV$^-$DLBCL）相比，非免疫缺陷性EBV$^+$DLBCL主要发生于老年男性群体中，中位年龄为71岁（范围为50~91岁），对治疗的应答率及预后差，并提出老年EBV$^+$DLBCL患者是一个独特的临床亚型。2008年，世界卫生组织（World Health Organization，WHO）将发生在年龄大于50岁的EBV$^+$的单克隆性大B细胞性LPD，且无已知免疫缺陷疾病或淋巴瘤病史的患者暂定为老年EBV$^+$DLBCL患者。由于年轻人群中也会出现EBV$^+$DLBCL患者[15-17]，在2016年WHO修订版中，将老年EBV$^+$DLBCL的命名修订为非特指EBV$^+$DLBCL（EBV$^+$DLBCL，not otherwise specified，EBV$^+$DLBCL-NOS）[1，18]。

## 2 EBV$^+$DLBCL–NOS的流行病学和临床表现特征

流行病学研究表明，相比于西方国家（<5%），亚洲及拉丁美洲DLBCL中EBV$^+$的比例较高（8.7%~11.4%）[14]。中国EBV$^+$DLBCL-NOS的发生率占DLBCL的3.8%~19.0%[19-25]，多见于南方地区[20，22-23，26]。不同国家发病率差异的具体原因和机制尚不清楚，推测与EBV流行毒株差异和遗传因素（如人类白细胞抗原类型）相关[1]。

EBV$^+$DLBCL-NOS在东亚人群中表现出独特的疾病特征[14，16，19-20，27]。临床上，EBV$^+$DLBCL-NOS大多发生在50岁以上患者中[28]，高峰年龄为75岁，但也可以发生于免疫功能正常的年轻人中，男女比例约为1.2~3.6∶1.0。EBV$^+$DLBCL-NOS患者的疾病分期通常较晚，约82%的患者有结外受累，包括消化道、皮肤、骨髓等部位[29]。EBV$^+$DLBCL-

NOS患者的乳酸脱氢酶（lactate dehydrogenase，LDH）水平高、国际预后指数（international prognostic index，IPI）评分高及体能状态差，存在B症状（包括发热、盗汗及体重减轻）的概率高[25，29-30]，因此预后差。多项研究[16-17，31-32]表明，年轻EBV$^+$DLBCL患者的预后显著优于老年患者。然而，IPI评分用于预测EBV$^+$DLBCL-NOS患者预后的价值有限[1]。在利妥昔单抗用于临床之前，Oyama等[32]认为年龄（≥70岁）和B症状是EBV$^+$DLBCL-NOS患者的两个独立危险因素，具有0（低危）、1（中危）和2（高危）个独立危险因素的患者中位OS分别为56、25和9个月，差异有统计学意义（$P$＜0.05）。在利妥昔单抗用于临床后，钟敏等[33]研究发现，Ann Arbor分期、IPI评分及Ki-67免疫染色阳性率为影响EBV$^+$DLBCL患者临床疗效的主要因素。此外，淋巴细胞计数＜1.0×10$^9$/L、CD30及生存素等均可能与患者的不良预后相关[27，34-35]。

## 3 EBV$^+$DLBCL的病理学诊断和鉴别诊断

EBV$^+$DLBCL-NOS患者的组织病理学特征并不十分鲜明，形态学谱系也比较宽泛[1，18]。大体形态上，肿瘤细胞可能表现出大细胞、中心母细胞、免疫母细胞或霍奇金样细胞的特征，呈弥漫性分布，或散在分布于大量反应性背景细胞中，类似于富于T细胞/组织细胞亚型[1]。肿瘤细胞通常表达B细胞抗原，包括CD19、CD20、CD22、CD79a和配对蛋白5。细胞起源上，90%的EBV$^+$DLBCL-NOS为非生发中心来源亚型，表现为多发性骨髓瘤癌基因1阳性而缺乏CD10/B细胞淋巴瘤6（B-cell lymphoma 6，BCL6）的表达[19，28，36]。此外，约42%的EBV$^+$DLBCL患者表达CD30[23]，且有时与CD15共表达，但缺乏其他经典霍奇金淋巴瘤的表型特征[18，37]。EBV$^+$DLBCL-NOS的诊断金标准为在异型B淋巴细胞中检测到EBV编码RNA（EBV encoded RNA，EBER）[14，21]，且除外某些特定的EBV$^+$淋巴瘤类型，如浆母细胞性淋巴瘤（plasmablastic lymphoma，PBL）、原发性渗出性淋巴瘤（primary effusion lymphoma，PEL）、人类疱疹病毒8型（human herpesvirus 8，HHV-8）相关的LPD、EBV$^+$黏膜与皮肤溃疡、慢性炎症相关性DLBCL（DLBCL associated with chronic inflammation，DLBCL-CI）等[7]。目前EBER的诊断阈值仍无统一标准。尽管2016版WHO血液及淋巴组织肿瘤分类[18]指出，肿瘤细胞EBER原位杂交阳性应＞80%，但既往研究采用的阈值从5%到80%不等，多以≥20%～50%界定为EBER阳性[14，17]。值得注意的是，一项纳入多项针对EBV$^+$DLBCL研究（8 249例患者）的meta分析[38]表明，不同的EBER阈值（10%、20%和50%）并不显著影响EBV$^+$DLBCL-NOS的患病率计算。

EBV$^+$DLBCL-NOS的诊断需要排除某些特殊类型的EBV相关淋巴瘤[1]，如PBL、PEL和DLBCL-CI。临床和病理学诊断的主要鉴别要点包括：① PBL为高度侵袭性淋巴瘤，预后差，多数患者有免疫缺陷病史[39]；病灶常侵犯口腔及消化道等部位[1，40]；病理学诊断上，淋巴瘤细胞常表达浆细胞分子标记而不表达CD20，且增殖指数高达90%～100%，约半数病例存在*MYC*基因重排[1]。② 多数PEL病例有免疫缺陷病史，有HHV-8病毒感染的证据，淋巴瘤细胞常侵及胸膜或心包腔等部位而不形成明显肿块，可表达CD45而不表达B细胞分子标记，且*MYC*、*BCL2*及*BCL6*重排通常阴性[1]。③ DLBCL-CI患者的中位年龄约70岁，有人工气胸治疗或慢性炎症性疾病（如结核病）史，而无免疫缺陷病病史[7]；肿块多出现在胸膜、胸壁或临近胸膜的肺部中，并伴相应部位的疼痛；淋巴瘤细胞的*TP*53基因突变和*MYC*基因扩增常见[1，7]。

## 4 EBV$^+$DLBCL–NOS的治疗现状及预后

目前，尚未有特定药物或方案获批用于EBV$^+$DLBCL-NOS患者的一线治疗。美国国立综合癌症网络（National Comprehensive Cancer Network，NCCN）和中国临床肿瘤学会（Chinese Society of Clinical Oncology，CSCO）指南并未针对EBV$^+$DLBCL-NOS患者提供特殊的治疗方案，因此一线治疗仍参考DLBCL-NOS的治疗方案，即采用含利妥昔单抗的免疫化疗方案[1]。既往CHOP方案（环磷酰胺＋多柔比星＋长春新碱＋泼尼松）在EBV$^+$DLBCL-NOS患

者[1]中的完全缓解（complete response，CR）率仅30%，5年总生存（overall survival，OS）率约25%。据报道，中国EBV$^+$DLBCL-NOS患者接受CHOP/R-CHOP方案治疗后的中位OS为9～37个月[17, 19, 21, 28]，中位无进展生存期（progression-free survival，PFS）为9.8～20.7个月[19]，3年OS率和PFS率均为25%左右[21]。Beltran等[1]总结了免疫化疗对EBV$^+$DLBCL-NOS患者的疗效情况（表1），提示含利妥昔单抗的免疫化疗方案可显著提高EBV$^+$DLBCL-NOS患者的生存率[33, 40]，然而仍显著差于EBV$^-$DLBCL患者[17, 29-30]。因此，提高这类患者的一线治疗效果仍是当前临床上未被满足的需求。此外，由于EBV$^+$DLBCL-NOS的发病率相对较低并存在地区分布的差异，对该特殊亚型的认知比较有限，也缺乏多中心、高质量的前瞻性临床研究，因此需要积极探索新的治疗方案。

## 5 EBV$^+$DLBCL–NOS的发病机制及新治疗方法

### 5.1 发病机制

有研究[41-42]表明，EBV癌基因可显著改变肿瘤细胞的基因表达，并诱导化疗耐药。EBV编码的蛋白质和非编码RNA（non-coding RNA，ncRNA）可激活细胞内多种致癌信号转导通路[43]，包括NF-κB、磷脂酰肌醇3-激酶（phosphatidylinositol 3-kinase，PI3K）/蛋白激酶B（protein kinase B，AKT）、Janus激酶/信号转导和转录激活因子（Janus kinase/signal transducer and activator of transcription，JAK/STAT）、丝裂原活化蛋白激酶（mitogen-activated protein kinase，MAPK）、转化生长因

表1 免疫化疗对EBV$^+$DLBCL–NOS患者的疗效汇总

**Tab. 1 A brief summary on the use of immunochemotherapy in patients with EBV$^-$positive DLBCL**

| Study | EBER | Regimen | N | OR/CR rate | OS |
|---|---|---|---|---|---|
| Oyama, 2007 | ＞50% | CHOP | 56 | 80%/66% | 5-year: 25% |
| Park, 2011 | ＞20% | CHOP | 25 | 72%/NR | 5-year: 48% |
| Beltran, 2011 | ＞20% | R-CHOP | 8 | NR/66% | 3-year: 40% |
| | | CHOP | 12 | NR/33% | 3-year: 40% |
| Ahn, 2014 | ＞50% | R-CHOP | 18 | 72%/61% | 3-year: 57% |
| Ok, 2014 | ＞10% | R-CHOP | 28 | 89%/NR | 5-year: 54% |
| Sato, 2014 | ＞30% | R-CHOP | 8 | 50%/25% | 3-year: 38% |
| | | CHOP | 3 | 33%/33% | 3-year: 0% |
| Lu, 2015 | ＞20% | R-CHOP | 35 | 66%/NR | 3-year: 30% |
| Song, 2015 | NR | R-CHOP | 8 | 63%/50% | 3-year: 70% |
| | | CHOP | 8 | 50%/38% | 3-year: 25% |
| Okamoto, 2016 | ＞20% | R-CHOP | 13 | NR | 4-year: 41% |
| Hong, 2017 | ＞20% | R-CHOP | 14 | NR | Median: 15.0 months |
| Beltran, 2018 | ＞20% | R-CHOP | 17 | 59%/71% | 5-year: 54% |
| | | CHOP | 16 | 31%/31% | 5-year: 38% |
| Liu, 2018 | ＞50% | R-CHOP | 6 | NR/50% | 2-year: 20% |
| | | CHOP | 3 | NR/50% | 2-year: 0% |
| Witte, 2019 | ＞50% | R-CHOP | 62 | 94%/67% | 2-year: 70% |
| Zhou, 2019 | ＞50% | R-CHOP | 22 | NR | Median: 29.0 months |
| Yoon, 2020 | ＞20% | I-R-CHOP | 24 | 66.7%/66.7% | Median: 20.9 months |

R: Rituximab； I: Ibrutinib； NR: Not reported.

子-β（transforming growth factor beta，TGF-β）等。例如，EBV编码的潜伏性膜蛋白2A（latent membrane protein 2A，LMP2A）可部分模拟B细胞受体（B-cell receptor，BCR）信号转导通路[44]，也可使细胞凋亡调节因子Bcl-xL和视网膜母细胞瘤相关蛋白1的表达异常而干扰B淋巴细胞的凋亡和细胞周期，与*MYC*癌基因及突变型细胞周期蛋白D3协同促进细胞存活和增殖[44]。因此，EBV$^+$DLBCL-NOS肿瘤细胞高表达CD30，显著表达Toll样受体和激活JAK/STAT通路[6, 12, 36, 45]。尽管体外实验[44, 46]发现，LMP1/2A可激活B淋巴细胞的布鲁顿氏酪氨酸激酶（Bruton's tyrosine kinase，BTK）通路；然而，体内研究发现，单独LMP1或LMP2A的表达无法导致B细胞恶性转变[42]，且EBV$^+$DLBCL-NOS肿瘤细胞的BTK通路活性呈现显著下调[36]。EBV$^+$DLBCL-NOS患者的基因组也存在大量致病性突变。例如，Liu等[47]通过DNA全外显子组测序技术，分析了11例中国EBV$^+$DLBCL-NOS患者，发现白血病NUP98融合伙伴蛋白1（11/11）、人丝氨酸蛋白酶3（10/11）、黏蛋白3A（9/11）、鱼脂肪酸去饱和酶6（9/11）和驱动蛋白结合1（8/11）基因存在高频突变。Zhou等[48]应用二代测序（next-generation sequencing，NGS）技术发现，9例中国EBV$^+$DLBCL-NOS肿瘤细胞中*MYC*基因突变最为显著，且与预后相关。最近，Gebauer等[49]利用全基因组和靶向扩增子测序技术，发现EBV$^+$DLBCL-NOS肿瘤细胞中染色质重塑分子富含AT结合域1A（45%）、赖氨酸甲基转移酶2A/2D（30%）、锚蛋白重复结构域11（32%）和Notch同源物2（32%）等存在高频突变，进一步的基因富集分析和功能注释提示，NF-κB、JAK/STAT和Wnt信号转导通路以及免疫过程如干扰素应答通路的异常，可能参与EBV$^+$DLBCL-NOS的发病过程[25]。由于EBV$^+$DLBCL-NOS的发病率较低，多数研究的样本数偏小，且大部分研究为回顾性分析，因此，目前仍未能了解EBV$^+$DLBCL-NOS患者*MYC*基因重排和“双打击”淋巴瘤的具体发生率[19, 48, 50]。

EBV$^+$DLBCL-NOS的另一重要发病原因是宿主免疫衰老导致机体免疫监视功能的缺失[41]。在T细胞功能缺陷的条件下，LMP1分子模拟CD40辅助受体分子将导致B细胞发生快速且致命性的细胞增殖和淋巴瘤发生[51]，且EBV$^+$LPD中有大量程序性死亡［蛋白］-1（programmed death-1，PD-1）阳性的淋巴细胞浸润[52]，提示免疫逃逸机制参与EBV$^+$LPD的发病过程。Yoon等[41]研究发现，老年EBV$^+$DLBCL患者的宿主免疫反应相关分子的拷贝数变异和基因表达谱改变，是区别于EBV$^-$DLBCL患者的关键分子特征，尤其是9p24.1染色体上的程序性死亡［蛋白］配体-2（programmed death ligand-2，PD-L2）。此外，EBV$^+$DLBCL-NOS肿瘤细胞高表达PD-L1/2，而低表达Ⅱ型反式激活蛋白和主要组织相容性复合体Ⅱ，提示抗原递呈系统的破坏也在肿瘤的发病过程中发挥一定的作用[36]。

### 5.2 *新治疗方案*

#### 5.2.1 BTK抑制剂

体外研究[53]发现，EBV导致B细胞的恶性转变部分依赖于BCR/BTK信号转导通路的异常激活，提示BTK抑制剂可能是治疗EBV$^+$DLBCL-NOS患者的有效药物。一项来自韩国的Ⅱ期临床研究[53]探索了BTK抑制剂伊布替尼联合R-CHOP治疗EBV$^+$DLBCL的有效性及安全性，但其结果显示，伊布替尼联合R-CHOP（I-RCHOP）治疗组的总体客观缓解率为66.7%，与R-CHOP治疗组（66.7%）持平。尽管在＜65岁的亚组中I-RCHOP较R-CHOP展现出更高的CR率（87.3%和68.8%），但差异并无统计学意义（$P$=0.53）。此外，在≥65岁的亚组中，I-RCHOP相比R-CHOP显著增加了治疗相关死亡率，其中4例患者出现罕见的感染但不伴有3~4度的粒细胞减少。鉴于该研究的阴性结果，BTK抑制剂联合R-CHOP一线治疗EBV$^+$DLBCL-NOS患者可能并不是理想的一线选择。

#### 5.2.2 组蛋白去乙酰化酶（histone deacetylases，HDAC）抑制剂

EBV的复制独立于胸苷激酶，因此依赖胸苷激酶抑制的传统抗病毒药物无法控制恶性B细

胞中的EBV复制[54]。然而，传统抗病毒药物联合HDAC抑制剂却有显著的抗肿瘤效应[54]。一项Ⅰ/Ⅱ期临床研究[54]使用具有HDAC活性的精氨酸丁酸盐和更昔洛韦联合治疗15例复发的EBV$^+$BCL患者，均取得较好疗效，其中4例获得CR。进一步研究[55]发现，HDAC抑制剂与更昔洛韦存在协同效应。此外，HDAC抑制剂可能通过降低EBV$^+$细胞株LMP1和c-MYC的表达而产生细胞毒性作用[56]。一项Ⅱ期临床研究[57]发现，6例难治性EBV$^+$DLBCL-NOS患者口服纳蒂诺他联合更昔洛韦治疗后，总反应率（overall response rate，ORR）和CR率分别为66%和33%。此外，EBV$^+$人类免疫缺陷病毒（human immunodeficiency virus，HIV）相关性DLBCL患者的预后更差，疾病进展迅速[58]。2018年，一项在美国完成的Ⅰ/Ⅱ期临床研究（AMC-075）[58]探究了伏立诺他联合R-EPOCH方案治疗高度侵袭性HIV相关性DLBCL患者的安全性及有效性，发现1例EBV$^+$HIV相关性DLBCL患者获得持久CR，而1例EBV$^+$HHV-8$^+$HIV相关性DLBCL患者治疗4个周期后获得部分缓解（partial response，PR）。然而，多数临床研究纳入的病例数过少，一线HDAC抑制剂的联合方案对于EBV$^+$DLBCL-NOS患者的有效性和安全性，尚有待更多的临床研究予以证实。

5.2.3 免疫检查点抑制剂

DLBCL-NOS患者的PD-L1表达率较低，仅8.9%～11.0%，而EBV$^+$DLBCL-NOS患者肿瘤细胞及肿瘤微环境中的PD-L1表达率高达41.0%～100.0%[59-60]。PD-L1表达与DLBCL患者的EBER阳性率、非生发中心来源亚型及不良预后相关[60]。含利妥昔单抗的治疗方案也部分依赖抗体介导的细胞毒性效应来实现。因此，通过恢复细胞毒性T细胞的扩增和杀伤活性，利用PD-1单抗靶向免疫检查点通路的治疗方案可能在EBV$^+$DLBCL-NOS患者中获得较好疗效[61]。尽管PD-1单抗单药在复发/难治性DLBCL患者中的ORR仅10%左右[62]，但是PD-1单抗联合化疗一线治疗DLBCL患者可能获得较好疗效[63]。2019年，Younes等[64]采用阿替利珠单抗联合R-CHOP一线治疗42例DLBCL患者，发现接受至少一剂阿替利珠单抗的40例DLBCL患者中，独立审评委员会评估的CR率为77.5%，PR率为10%，研究者评估的2年PFS率和OS率分别为74.9%和86.4%。尽管不良反应导致15例患者（36%）的治疗终止（主要包括3例中性粒细胞减少、3例脂肪酶升高和2例淀粉酶升高），不良反应总体可控、可逆，且疗效是持续的。2020年，Smith等[63]采用帕博利珠单抗联合R-CHOP一线治疗30例DLBCL患者，结果ORR和CR率分别为90%和77%，2年PFS率和OS率分别为83%和84%，并且未显著增加严重不良反应的发生率，提示PD-1/PD-L1单抗可以安全且有效地加入到DLBCL的一线治疗中，并且该研究中PD-L1（＞50%）高表达的2例EBV$^+$DLBCL患者在一线治疗后均获得CR并处于持续无进展状态。由于缺乏随机对照临床试验，且未对DLBCL患者进行选择性治疗，因此含免疫检查点抑制剂的方案是否能真正改善EBV$^+$DLBCL-NOS患者的预后尚待进一步确认。目前，PD-1单抗治疗淋巴瘤的良好安全性和潜在有效性，已经引起了临床医师的关注。美国临床研究网站显示，当前已有多项针对淋巴瘤患者采用靶向PD-1单抗联合免疫治疗的临床研究（表2）。

5.2.4 其他探索中的治疗方法

5.2.4.1 细胞疗法

靶向LMP-1的嵌合抗原受体T细胞（chimeric antigen receptor T-cell，CAR-T）疗法在鼻咽癌中取得了初步疗效[65]，有望在EBV$^+$DLBCL患者中得到应用。Bollard等[66]使用过表达*LMP*基因的腺病毒转染树突状细胞体外诱导扩增LMP-1/2特异性细胞毒性T淋巴细胞治疗50例EBV$^+$淋巴瘤患者，有效率达64%，但该疗法目前仍处于临床探索阶段。

5.2.4.2 抗蛋白酶体药物

EBV$^+$DLBCL多为激活的B细胞样（activated B-cell，ABC）亚型，蛋白酶体抑制剂硼替佐米可以诱导EBV$^+$B细胞的凋亡[67]。然而，硼替佐米联合免疫化疗没有在ABC亚型DLBCL患者中取得令人满意的临床疗效[68-69]。

表2 一线应用PD-1单抗治疗淋巴瘤患者的临床研究汇总

Tab. 2 Summary of clinical studies on first-line treatment of lymphoma patients with PD-1 antibody

| Registration Number | PD-1 antibody | Regimen | Study start date | Study Type | Patients |
|---|---|---|---|---|---|
| NCT03258567 | Nivolumab | - | 2018.04.26 | Phase Ⅱ | $EBV^+$PLD/NHL |
| NCT03990961 | Pembrolizumab | - | 2019.09.04 | Phase Ⅱ | PD-$L1^+$DLBCL |
| NCT03749018 | Nivolumab | DA-EPOCH-R | 2019.01.02 | Phase Ⅱ | High-grade BCL |
| NCT03892044 | Nivolumab | Duvelisib | 2019.11.05 | Phase Ⅰ | Richter syndrom/transformed DLBCL |
| NCT04181489 | Sintilimab | R-CHOP | 2019.01.01 | Phase Ⅱ | $EBV^+$ DLBCL-NOS |
| NCT04023916 | Sintilimab | R-CHOP | 2019.12.01 | Phase Ⅱ | PD-$L1^+$ and *TP*$53^{mut}$ DLBCL |
| NCT04058470 | Toripalimab | R-CHOP | 2020.04.24 | Phase Ⅰb/Ⅱ | DLBCL/FL3b/$EBV^+$DLBCL/ALK+ALCL of the elderly |

FL: Follicular lymphoma; ALK: Anaplastic lymphoma kinase; PLD: Lymphoproliferative disorders.

5.2.4.3 PI3K和哺乳动物雷帕霉素靶蛋白（mammalian target of rapamycin，mTOR）抑制剂

EBV编码蛋白可激活肿瘤细胞内的PI3K/AKT信号转导通路[43]，因此，靶向PI3K激酶通路也可能有潜在的应用价值。Sang等[70]研究发现，在小鼠模型中双重阻断PI3K/AKT/mTOR信号转导通路可抑制移植后$EBV^+$淋巴瘤，延长动物的存活期。此外，Wang等[71]研究发现，mTOR抑制剂木脂素B对$EBV^+$LPD也可能有潜在的治疗价值。

5.2.4.4 其他靶点

DLBCL患者肿瘤细胞高表达CD30和CD38。因此，维布妥昔和雷妥尤单抗也可能成为潜在的治疗靶点。然而，评估维布妥昔单药治疗$CD30^+$的$EBV^+$DLBCL患者（NCT01671813）的一项临床研究因医药企业停止资助而被终止，维布妥昔联合利妥昔单抗治疗$CD30^+$或$EBV^+$淋巴瘤患者（NCT01805037）的临床研究也因为缺乏研究经费而被终止。此外，$EBV^+$B细胞高表达NK细胞受体NKG2D的配体，即维甲酸早期诱导蛋白1，动物实验[51]已证明，靶向NKG2D可显著抑制$EBV^+$B细胞增殖，靶向NKG2D疗法是否同样在人体中有效尚需进一步验证。

## 6 结语

综上所述，EBV感染和机体免疫功能异常在$EBV^+$DLBCL-NOS的发生、发展过程中发挥关键性作用。临床上对$EBV^+$DLBCL-NOS患者的疾病特征、治疗应答情况及预后模式的认识有限，需要更大样本量数据结果的证实。$EBV^+$DLBCL-NOS是一种独特的DLBCL亚型，今后仍需要大量的基础及临床研究，在探究其生物学特性的同时寻找有效的靶向治疗药物。然而，$EBV^+$DLBCL-NOS肿瘤微环境中PD-1/PD-L1/2信号转导通路激活参与疾病的发生、发展，为探索靶向PD1/PD-L1的免疫疗法提供了良好的理论依据。此外，也期待靶向EBV编码蛋白的细胞治疗能显著改善$EBV^+$DLBCL-NOS患者的生存。

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