

• 病例报告 •

## 泽布替尼联合利妥昔单抗及来那度胺治疗心脏和肾脏大包块的老年弥漫大 B 细胞淋巴瘤 1 例并文献复习

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**[摘要]** 本研究主要探讨泽布替尼联合利妥昔单抗及来那度胺治疗虚弱老年弥漫大 B 细胞淋巴瘤(DLBCL)患者的疗效及安全性。回顾性分析上海交通大学医学院附属瑞金医院 2023 年 1 月收治的 1 例心脏和肾脏大包块且并发心房颤动的虚弱老年 DLBCL 患者的治疗经过,并进行文献复习。患者,男,68 岁,因腰痛,发现肾脏大包块,进一步行 PET-CT 检查,发现心脏、胃壁、肾脏、腹腔等多部位受累,胃壁活组织检查确诊为 DLBCL,该患者高肿瘤负荷且伴有多个不良预后因素,接受泽布替尼联合利妥昔单抗及来那度胺方案治疗后疾病快速获得缓解,且缓解时间持久,同时不良反应可耐受。

**[关键词]** 泽布替尼;来那度胺;弥漫大 B 细胞淋巴瘤

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## Zanubrutinib in combination with rituximab and lenalidomide for the treatment of an elderly diffuse large B-cell lymphoma with large cardiac and renal masses: a case and review of the literature

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**Abstract** This study focuses on the efficacy and safety of zanubrutinib combined with rituximab and lenalidomide in the treatment of frail elderly patients with diffuse large B-cell lymphoma(DLBCL). We retrospectively analyzed the treatment history of a frail elderly DLBCL patient with large masses in heart and kidney and concomitant with atrial fibrillation who was admitted to Ruijin Hospital of Shanghai Jiaotong University School of Medicine in January 2023. We also performed a literature review. A 68-year-old male with lumbago was found to have a large renal mass. Further PET-CT examination revealed multiple sites of cardiac, gastric wall, renal, and abdominal involvement, and gastric wall biopsy confirmed the diagnosis of DLBCL. This patient with a high tumor burden and multiple adverse prognostic factors was given zanubrutinib combined with rituximab and lenalidomide regimen. A rapid disease remission was obtained and the remission was durable. Furthermore, the adverse effects were tolerable.

**Key words** zanubrutinib; lenalidomide; diffuse large B-cell lymphoma

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弥漫大 B 细胞淋巴瘤 (diffuse large B-cell lymphoma, DLBCL) 是非霍奇金淋巴瘤 (non Hodgkin lymphoma, NHL) 中最常见的淋巴瘤且具有高度异质性, 占有 NHL 的 30%~40%<sup>[1]</sup>。治疗 DLBCL 的经典方案为利妥昔单抗、环磷酰胺、阿霉素、长春新碱及泼尼松四药组成的方案 (R-CHOP 方案), 但高危患者的长期生存率仍低于 40%<sup>[2]</sup>, 尤其是虚弱老年 DLBCL 患者, 肿瘤侵袭性高, 体能状态差, 并发症多, 化疗耐受性差, 治疗方案有限, 预后更差<sup>[3]</sup>。目前认为对老年 DLBCL 进行分层治疗的有效工具是老年综合评估 (comprehensive geriatric assessment, CGA)<sup>[4]</sup>。临床中可采用简易版的 CGA 评估方法<sup>[5]</sup>, 主要从日常生活能力 (ADL)、工具性日常活动能力 (IADL)、合并症等方面对老年患者进行全面评估, 可将老年 DLBCL 患者分为适合化疗 (fit) 组、不适合化疗 (unfit) 组和脆弱 (frail) 组 3 个预后不同的亚组。对于 fit 组患者, R-CHOP 方案仍是其标准的治疗方案, 其 10 年无进展生存 (progression-free survival, PFS) 率和总生存 (overall survival, OS) 率分别为 36.5% 和 43.5%<sup>[2]</sup>。对于 unfit 组的老年患者, 无心脏基础疾病的患者, 利妥昔单抗联合减量的 CHOP (R-miniCHOP) 方案治疗, 2 年 PFS 率为 47%, 2 年 OS 率为 59%, 被美国国立综合癌症网络 (NCCN) 指南推荐作为 unfit 组患者的一线治疗方案<sup>[6]</sup>; 有心脏疾病的患者, 考虑到治疗相关并发症主要来源于化疗药物的心脏毒性, 常常会选择替代蒽环类药物, 如脂质体多柔比星<sup>[7]</sup>、吉西他滨<sup>[8]</sup>、依托泊苷<sup>[9]</sup>, 其疗效及安全性均可。对于 frail 组老年 DLBCL 患者, 减弱强度化疗患者 2 年 OS 率为 28%, 姑息性治疗患者的 2 年 OS 率仅为 21%<sup>[10]</sup>。故针对此类患者亟需寻找安全高效的治疗方案。现报道 1 例泽布替尼联合利妥昔单抗及来那度胺 (ZR2) 的无化疗的靶向 (chemo-free) 方案成功治疗 1 例大肿瘤负荷伴心脏大包块的 frail 组老年初发高危 DLBCL 患者。

## 1 病例资料

患者, 男, 68 岁。2023 年 1 月患者无明显诱因出现活动后腰部疼痛、胸闷。完善腹部 CT 检查示左肾邻近肾实质团块、肾门旁增大淋巴结。PET-CT: 左、右心房受累、纵隔多发淋巴结肿大, 氟-脱氧葡萄糖 (FDG) 代谢增高; 胃壁增厚受累, 左肾中下极肿块, 腹腔、后腹膜多发肿块, FDG 代谢增高, 考虑淋巴瘤可能 (图 1)。

胃镜检查见胃体多发溃疡, 病理结果为 DLBCL, 非生发中心亚型 (non-germinal center B-cell-like lymphoma, non-GCB)。免疫组织化学: CD20(+), CD22(+), CD19(+), CD79a(+), C-MYC (约 60%+), BCL-2 (5%+), BCL-6 (90%+),

MUM-1 (约 50%+), Ki67 (约 100%+), CD37(+), CD38 (少量+), CD47 (部分弱+), P53 (约 90%+), CD3(-), CD5(-), CD21(-), CD23(-), CD10(-), CyclinD1(-), AE1/AE3(-), CD30(-); EBER(-)。FISH 结果: BCL6(+), BCL2(-), C-MYC(-), IRF4(-), 发现 17p- (32% 细胞可见 17p 缺失)。入院查体: 神志清, 精神差, 心率 115 次/min, 心律不齐 (心房颤动), 血压 121/73 mmHg (1 mmHg=0.133 kPa), 浅表淋巴结未及肿大, 双肺呼吸音粗, 未闻及干湿性啰音, 腹软, 无压痛及反跳痛, 下肢中度凹陷性水肿。实验室指标: 白细胞  $8.60 \times 10^9/L$ , 血红蛋白 106 g/L, 血小板  $313 \times 10^9/L$ 。血生化: 乳酸脱氢酶 328 IU/L (参考范围: 120~250 IU/L), 肝肾功、电解质指标正常。乙型肝炎、丙肝病毒抗体、艾滋病毒抗体均阴性。EBV 病毒-DNA: 阴性。氨基末端 B 型利钠肽前体: 2 815 pg/mL (参考范围: 5~349 pg/mL)。骨髓涂片、骨髓流式及骨髓活组织检查: 均未见淋巴瘤细胞累及。心电图: 心房颤动, T 波改变。心脏彩超: 房间隔见低回声团块 (大小约 56 mm × 25 mm), 累及左、右心房顶部; 前心包内另见低回声团块 (之一大小约 20 mm × 42 mm), 左室射血分数 55%。诊断: DLBCL, non-GCB 型, IV 期 A, 美国东部协作肿瘤组 (eastern cooperative oncology group, ECOG) 评分 3 分, 国际预后指数 (international prognostic index, IPI) 评分 5 分。患者年龄较大, 淋巴瘤肿瘤累及心脏并发心房颤动, 心功能差, 体能状态差, CGA 4 分, 患者为 frail 组。首次治疗时, 在心电监护下给予无化疗的靶向治疗方案 ZR2 (泽布替尼 160 mg, bid, po; 利妥昔单抗 375 mg/m<sup>2</sup>; 来那度胺 25 mg, +1~+10 d, po; 21 d 为 1 个疗程)。期间服用复方磺胺甲恶唑及阿昔洛韦片预防卡氏肺孢子虫和巨细胞病毒感染。整个治疗过程中, 未出现快室率心房颤动事件发生。1 个疗程后复查心电图: 房性早搏, I 度房室传导阻滞。2 个疗程后心脏彩超: 左房增大, 轻度三尖瓣关闭不全, 左室射血分数 63%。3 个疗程后 PET-CT 评估 (图 2): Deauville 评分: 3 分, Lugano 评分: 完全缓解 (complete response, CR)。继续 ZR2 方案治疗 3 疗程。6 疗程后 PET-CT 评估: 腹主动脉左侧、左肾周病变代谢较前减低, 范围明显缩小; Deauville 评分: 2 分, Lugano 评分: CR。后患者来那度胺口服维持治疗。截至末次随访 (2023 年 12 月), 治疗结束后 6 个月, 患者仍保持 CR 状态。

## 2 讨论

DLBCL 的发病率随着年龄的增长而逐渐增高<sup>[11]</sup>。DLBCL 患者的中位发病年龄在发达国家已经超过 65 岁<sup>[12]</sup>; 而在中国, 50% 以上的 DLBCL

患者均在65岁以上<sup>[13]</sup>。在利妥昔单抗时代,R-CHOP作为一线的标准治疗方案,年轻患者5年OS率可达90%<sup>[14]</sup>,而老年患者5年OS率仅为58%<sup>[3]</sup>。老年预后差的主要原因如下:一方面,老年DLBCL多数发病即处于进展期,肿瘤侵袭性高。在Aoki等<sup>[15]</sup>的研究中,>70岁的DLBCL患者中,有超过50%的患者处在Ann Arbor分期Ⅲ~Ⅵ期且乳酸脱氢酶高于正常;在Meguro等<sup>[16]</sup>的研究中,>60%的老年DLBCL患者出现乳酸脱氢酶的升高,接近50%的患者Ann Arbor分期处于Ⅲ~Ⅵ期。另外,老年DLBCL患者因自身营养状态不佳,器官功能有不同程度的减退,且并发症多,无法耐受标准剂量的R-CHOP方案化疗。针对老年DLBCL患者尤其是frail组老年患者寻找安全有效的治疗方案仍是一项挑战。

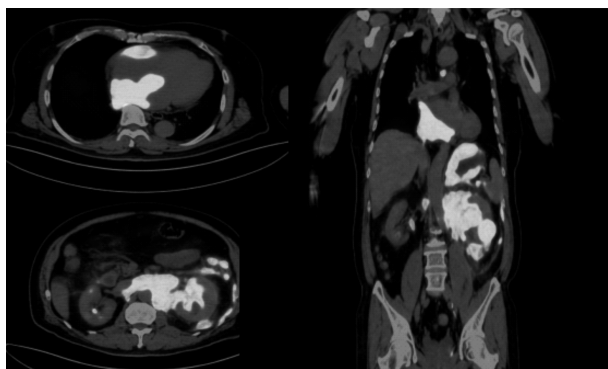
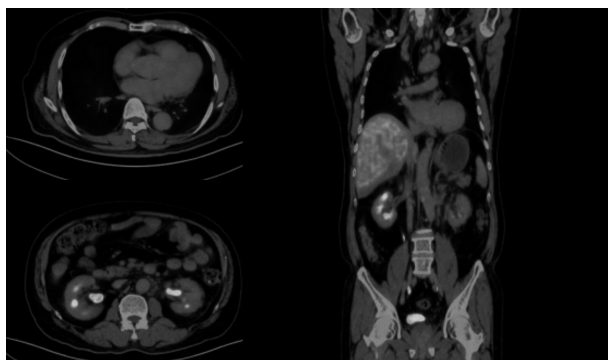


图1 治疗前PET-CT图像



注:与前片比较,后腹膜主动脉旁及左肾门片絮状软组织灶,代谢较前减低,形态退缩;其余前片所见异常高代谢病灶,本次显像均已消失。

图2 治疗后PET-CT图像

近年来,随着对老年DLBCL发病机制的研究,新型靶向药物多尝试应用于老年患者。non-GCB亚型DLBCL的发病多有B细胞受体(BCR)信号通路的慢性活化而导致B细胞恶性肿瘤的生存、进展、增殖<sup>[17]</sup>。布鲁顿氏酪氨酸激酶(Bruton's tyrosine kinase, BTK)参与上游BCR信号通路<sup>[18]</sup>。而BCR信号通路成员主要为BTK,故

BTK是CXCL12/CXCR4轴的主要作用靶点<sup>[19]</sup>。BTK抑制剂能下调NF- $\kappa$ B信号通路进而杀伤肿瘤细胞<sup>[20]</sup>。研究显示,BTK抑制剂伊布替尼无论在体外和体内均可抑制CXCR4表达,可克服骨髓基质细胞介导的DLBCL细胞耐药<sup>[21]</sup>。来那度胺是一种免疫调节剂的靶向药物,能够下调BCR下游的干扰素调节因子4(IRF4)和MYD88信号通路,导致干扰素- $\beta$ 分泌增加和NF- $\kappa$ B活性降低,进而发挥抗肿瘤作用<sup>[22]</sup>。此外,据报道,JAK-STAT通路基因突变上调与DLBCL接受基于利妥昔单抗的免疫化疗患者的不良临床结果相关<sup>[23]</sup>。然而,上调的JAK-STAT通路可能被来那度胺作用,并在应答者中富集,表明来那度胺可能克服DLBCL致癌途径的不利影响<sup>[24]</sup>。同时,数据表明来那度胺的免疫调节特性(增加自然杀伤细胞和T细胞活化以及改善免疫突触)可克服B细胞淋巴瘤中的利妥昔单抗耐药性<sup>[22]</sup>。BTK抑制剂也能够下调IRF4,与来那度胺发挥协同作用<sup>[25]</sup>,故临床前研究表明,当BTK抑制剂和来那度胺联合使用时,DLBCL模型中的抗淋巴瘤活性增加。SMART研究针对初诊non-GCB亚型DLBCL患者,应用伊布替尼、利妥昔单抗、来那度胺(IR2)联合治疗2个月,86%的受试者治疗有效,CR率为36%<sup>[26]</sup>。另有研究发现,应用IR2方案治疗老年(>75岁)初发DLBCL的患者,CR率为56.7%,客观缓解率(objective response rate, ORR)为66.7%,2年PFS率为53.3%,2年OS率为66.7%,无明显不良反应<sup>[27]</sup>。得克萨斯大学安德森癌症中心报道采用IR2方案2周期后序贯6周期化疗(R-CHOP或R-EPOCH方案)治疗新诊断的non-GCB亚型老年(中位年龄64岁)DLBCL患者,结果显示2周期IR2方案治疗后,患者ORR为84.6%,且不良反应可控<sup>[28]</sup>。可见,BTK抑制剂联合来那度胺和利妥昔单抗的方案治疗老年DLBCL是一种安全、有效、低毒的方案,为老年DLBCL尤其是不耐受化疗的患者提供了新的治疗选择。

本例患者为老年男性,诊断时存在多个不良预后因素:年龄>65岁、non-GCB亚型、高IPI、多结外病变、Ann Arbor分期Ⅳ期。除此之外,患者心脏大肿瘤包块并发心房颤动,经CGA评估,患者归为frail组。考虑到伊布替尼治疗患者中因脱靶效应<sup>[29]</sup>导致心房颤动发生率<sup>[30]</sup>,故选用我国自主研发的新一代强效BTK抑制剂泽布替尼,泽布替尼具有高度的选择性和特异性,脱靶效应发生率低。我们选择在严密心电监护下应用ZR2方案治疗。近期疗效显著,1个疗程后患者因原发病所致的心房颤动转为窦性心律且心脏占位明显缩小,2个疗程后心脏大肿瘤包块消退。3个疗程后获得CR,同时血液学不良反应可控,表明该治疗方案在

本例患者中的有效性及安全性均较好。即使有心房颤动并且心脏受到肿瘤侵犯的患者,在临床密切监测下,应用 ZR2 方案治疗可尝试。但 ZR2 去化疗方案在老年虚弱 DLBCL 患者中的安全性及有效性仍需要大样本的数据验证。

对于 frail 组的化疗不耐受的老年 DLBCL 患者,去化疗方案是未来的希望。ZR2 方案为这类 DLBCL 患者提供了一种新的治疗选择,亦可作为 R-CHOP 免疫化疗前的新药诱导,以达到 Chemo-free+短程化疗模式,甚至是对那些肿瘤累及心脏的老年 DLBCL 患者,在严密心电监护下 ZR2 方案可作为尝试的优先方案。应用 ZR2 方案不用承受化疗药物所致严重胃肠反应、严重骨髓抑制等不良反应,且泽布替尼及来那度胺口服方便,依从性好,此方案安全有效,值得开展前瞻性临床研究进一步验证其在老年 frail 组患者中的疗效和安全性。

**利益冲突** 所有作者均声明不存在利益冲突

## 参考文献

- [1] Swerdlow SH, Campo E, Pileri SA, et al. The 2016 revision of the World Health Organization classification of lymphoid neoplasms [J]. *Blood*, 2016, 127 (20): 2375-2390.
- [2] Coiffier B, Thieblemont C, Van Den Neste E, et al. Long-term outcome of patients in the LNH-98.5 trial, the first randomized study comparing rituximab-CHOP to standard CHOP chemotherapy in DLBCL patients; a study by the Groupe d'Etudes des Lymphomes de l'Adulte [J]. *Blood*, 2010, 116 (12): 2040-2045.
- [3] Feugier P, Van Hoof A, Sebban C, et al. Long-term results of the R-CHOP study in the treatment of elderly patients with diffuse large B-cell lymphoma; a study by the Groupe d'Etude des Lymphomes de l'Adulte [J]. *J Clin Oncol*, 2005, 23(18): 4117-4126.
- [4] Bai JF, Han HX, Feng R, et al. Comprehensive geriatric assessment (CGA): a simple tool for guiding the treatment of older adults with diffuse large B-cell lymphoma in China [J]. *Oncologist*, 2020, 25 (8): e1202-e1208.
- [5] Olivieri A, Gini G, Bocci C, et al. Tailored therapy in an unselected population of 91 elderly patients with DLBCL prospectively evaluated using a simplified CGA [J]. *Oncologist*, 2012, 17(5): 663-672.
- [6] Zelenetz AD, Gordon LI, Abramson JS, et al. NCCN Guidelines Insights: B-Cell Lymphomas, Version 3. 2019 [J]. *J Natl Compr Canc Netw*, 2019, 17(6): 650-661.
- [7] Luminari S, Viel E, Ferreri AJM, et al. Nonpegylated liposomal doxorubicin combination regimen in patients with diffuse large B-cell lymphoma and cardiac comorbidity. Results of the HEART01 phase II trial conducted by the Fondazione Italiana Linfomi [J]. *Hematol Oncol*, 2018, 36(1): 68-75.
- [8] Michalarea V, Low R, Kirkwood AA, et al. Excellent outcomes using rituximab, gemcitabine, cyclophosphamide, vincristine, prednisolone (R-GCVP) in patients with DLBCL and cardiac comorbidities [J]. *Hematol Oncol*, 2019, 37(S2): 425-426.
- [9] Storti S, Spina M, Pesce EA, et al. Rituximab plus bendamustine as front-line treatment in frail elderly (> 70 years) patients with diffuse large B-cell non-Hodgkin lymphoma: a phase II multicenter study of the Fondazione Italiana Linfomi [J]. *Haematologica*, 2018, 103(8): 1345-1350.
- [10] Boslooper K, Kibbelaar R, Storm H, et al. Treatment with rituximab, cyclophosphamide, doxorubicin, vincristine and prednisolone is beneficial but toxic in very elderly patients with diffuse large B-cell lymphoma: a population-based cohort study on treatment, toxicity and outcome [J]. *Leuk Lymphoma*, 2014, 55 (3): 526-532.
- [11] 李江涛, 张春丽, 冯茹, 等. 老年综合评估积分在高龄弥漫大 B 细胞淋巴瘤患者中的临床意义 [J]. *中华老年医学杂志*, 2019, 38(2): 170-175.
- [12] 李江涛, 刘辉, 范芸, 等. 老年初诊弥漫性大 B 细胞淋巴瘤患者临床特点回顾性分析 [J]. *中华老年医学杂志*, 2016, 35(2): 201-204.
- [13] Miller KD, Siegel RL, Lin CC, et al. Cancer treatment and survivorship statistics, 2016 [J]. *CA Cancer J Clin*, 2016, 66(4): 271-289.
- [14] Yang QP, Zhang WY, Yu JB, et al. Subtype distribution of lymphomas in Southwest China; analysis of 6, 382 cases using WHO classification in a single institution [J]. *Diagn Pathol*, 2011, 6: 77.
- [15] Aoki K, Takahashi T, Tabata S, et al. Efficacy and tolerability of reduced-dose 21-day cycle rituximab and cyclophosphamide, doxorubicin, vincristine and prednisolone therapy for elderly patients with diffuse large B-cell lymphoma [J]. *Leuk Lymphoma*, 2013, 54(11): 2441-2447.
- [16] Meguro A, Ozaki K, Sato K, et al. Rituximab plus 70% cyclophosphamide, doxorubicin, vincristine and prednisone for Japanese patients with diffuse large B-cell lymphoma aged 70 years and older [J]. *Leuk Lymphoma*, 2012, 53(1): 43-49.
- [17] Domanska UM, Kruizinga RC, Nagengast WB, et al. A review on CXCR4/CXCL12 axis in oncology; no place to hide [J]. *Eur J Cancer*, 2013, 49(1): 219-230.
- [18] Zhang Y, Zhao X, Tao J. Epigenetics, c-Myc and aggressive B-cell lymphomas [J]. *Oncotarget*, 2012, 3 (11): 1264-1265.
- [19] Aw A, Brown JR. Current Status of Bruton's Tyrosine Kinase Inhibitor Development and Use in B-Cell Malignancies [J]. *Drugs Aging*, 2017, 34(7): 509-527.
- [20] Davis RE, Ngo VN, Lenz G, et al. Chronic active B-cell-receptor signalling in diffuse large B-cell lymphoma [J]. *Nature*, 2010, 463(7277): 88-92.

- identifies a more aggressive NK cell proliferation[J]. Blood Cancer J, 2018, 8(6):51.
- [7] Bárcena P, Jara-Acevedo M, Tabernero MD, et al. Phenotypic profile of expanded NK cells in chronic lymphoproliferative disorders; a surrogate marker for NK-cell clonality [J]. Oncotarget, 2015, 6 (40): 42938-42951.
- [8] Pastoret C, Desmots F, Drillet G, et al. Linking the KIR phenotype with STAT3 and TET2 mutations to identify chronic lymphoproliferative disorders of NK cells[J]. Blood, 2021, 137(23):3237-3250.
- [9] Herling M, Braun T. Tracing the roots of CLPD-NK by TET2 and STAT3 [J]. Blood, 2021, 137 (23): 3156-3158.
- [10] Jerez A, Clemente MJ, Makishima H, et al. STAT3 mutations indicate the presence of subclinical T-cell clones in a subset of aplastic anemia and myelodysplastic syndrome patients[J]. Blood, 2013, 122(14): 2453-2459.
- [11] Sheikh S, Jahangir S, Khan S, et al. Chronic Lymphoproliferative Disorder of Natural Killer Cells; A Rare Event[J]. Cureus, 2020, 12(9):e10353.
- [12] Barilà G, Calabretto G, Teramo A, et al. T cell large granular lymphocyte leukemia and chronic NK lymphocytosis[J]. Best Pract Res Clin Haematol, 2019, 32 (3):207-216.
- [13] Kawakami T, Sekiguchi N, Kobayashi J, et al. STAT3 mutations in natural killer cells are associated with cytopenia in patients with chronic lymphoproliferative disorder of natural killer cells [J]. Int J Hematol, 2019, 109(5):563-571.
- [14] Gasparini VR, Binatti A, Coppe A, et al. A high definition picture of somatic mutations in chronic lymphoproliferative disorder of natural killer cells[J]. Blood Cancer J, 2020, 10(4):42.
- [15] Zhang R, Shah MV, Loughran TP Jr. The root of many evils; indolent large granular lymphocyte leukaemia and associated disorders[J]. Hematol Oncol, 2010, 28(3):105-117.
- [16] Lamy T, Moignet A, Loughran TP Jr. LGL leukemia: from pathogenesis to treatment[J]. Blood, 2017, 129 (9):1082-1094.
- [17] Lamy T, Loughran TP Jr. How I treat LGL leukemia [J]. Blood, 2011, 117(10):2764-2774.
- [18] Zaja F, Baldini L, Ferreri AJ, et al. Bendamustine salvage therapy for T cell neoplasms[J]. Ann Hematol, 2013, 92(9):1249-1254.
- [19] Fleischmann R, Kremer J, Cush J, et al. Placebo-controlled trial of tofacitinib monotherapy in rheumatoid arthritis[J]. N Engl J Med, 2012, 367(6):495-507.
- [20] Poullot E, Zambello R, Leblanc F, et al. Chronic natural killer lymphoproliferative disorders; characteristics of an international cohort of 70 patients[J]. Ann Oncol, 2014, 25(10):2030-2035.

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- [21] 吴凌, 张翼鹭, 夏冰, 等. 依布替尼通过新型途径克服弥漫大 B 细胞淋巴瘤细胞耐药机制的研究[J]. 中华血液学杂志, 2017, 38(12):1036-1042.
- [22] Ramsay AG, Clear AJ, Kelly G, et al. Follicular lymphoma cells induce T-cell immunologic synapse dysfunction that can be repaired with lenalidomide; implications for the tumor microenvironment and immunotherapy[J]. Blood, 2009, 114(21):4713-4720.
- [23] Morin RD, Assouline S, Alcaide M, et al. Genetic landscapes of relapsed and refractory diffuse large B-cell lymphomas [J]. Clin Cancer Res, 2016, 22 (9): 2290-2300.
- [24] Hartert KT, Wenzl K, Krull JE, et al. Targeting of inflammatory pathways with R2CHOP in high-risk DLBCL[J]. Leukemia, 2021, 35(2):522-533.
- [25] Yang Y, Shaffer AL 3rd, Emre NC, et al. Exploiting synthetic lethality for the therapy of ABC diffuse large B cell lymphoma[J]. Cancer Cell, 2012, 21(6): 723-737.
- [26] Westin JR, Nastoupil LJ, Fayad L, et al. Smart start: rituximab, lenalidomide, and ibrutinib alone and in combination with standard chemotherapy for patients with newly diagnosed diffuse large B-cell lymphoma: final phase II results[J]. Blood, 2019, 134(Suppl 1):1581.
- [27] Xu PP, Shi ZY, Qian Y, et al. Ibrutinib, rituximab, and lenalidomide in unfit or frail patients aged 75 years or older with de novo diffuse large B-cell lymphoma: a phase 2, single-arm study[J]. Lancet Healthy Longev, 2022, 3(7):e481-e490.
- [28] Westin JR, Nastoupil L, Hagemeister F, et al. Smart start: final results of rituximab, lenalidomide, and ibrutinib lead in prior to combination with chemotherapy for patients with newly diagnosed diffuse large B-cell lymphoma[J]. J Clin Oncol, 2019, 37(S15):7508.
- [29] Ahn IE. Cardiovascular adverse events of ibrutinib [J]. Blood, 2019, 134(22):1881-1882.
- [30] Munir T, Brown JR, O'Brien S, et al. Final analysis from RESONATE: Up to six years of follow-up on ibrutinib in patients with previously treated chronic lymphocytic leukemia or small lymphocytic lymphoma[J]. Am J Hematol, 2019, 94(12):1353-1363.

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