·专家述评·

布鲁顿酪氨酸激酶抑制剂治疗原发中枢神经系统淋巴瘤的研究进展

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摘要 原发中枢神经系统淋巴瘤(PCNSL)是一种高度侵袭性结外弥漫大B细胞淋巴瘤。尽管其对放化疗敏感,但基于大剂量甲氨蝶呤的传统标准治疗方案仍面临药物毒性大、复发率高及老年患者耐受性差等挑战。鉴于PCNSL高频伴发*MYD88*与*CD79B*突变,具有优异血脑屏障穿透能力的布鲁顿酪氨酸激酶抑制剂(BTKi)有望成为改善其预后的重要精准治疗策略。本文综述了BTKi在PCNSL治疗中的最新临床进展。

关键词 布鲁顿酪氨酸激酶抑制剂; 原发性中枢神经系统淋巴瘤; 治疗进展
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Research progress of Bruton's tyrosine kinase inhibitors in the treatment of primary central nervous system lymphoma

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Abstract Primary central nervous system lymphoma (PCNSL) is a highly aggressive extranodal diffuse large B-cell lymphoma. Although sensitive to chemoradiotherapy, traditional standard treatment regimens based on high-dose methotrexate still face challenges, such as high toxicity, high recurrence rate, and poor tolerance in older patients. Given the high frequency of *MYD88* and *CD79B* mutations in PCNSL, Bruton's tyrosine kinase inhibitors (BTKi), with their excellent blood-brain-barrier penetration capabilities, are expected to become an important precision treatment strategy for improving prognosis. In this article, the latest clinical progress of BTKi in the treatment of PCNSL is reviewed.

Keywords Bruton's tyrosine kinase inhibitors; primary central nervous system lymphoma; treatment progress

原发中枢神经系统淋巴瘤(primary central nervous system lymphoma,PCNSL)是一种局限于大脑、脊髓及软脑膜的高度侵袭性非霍奇金B细胞淋巴瘤,最常见的病理类型为大B细胞淋巴瘤(large B-cell lymphoma,LBCL)[1]。2022年,世界卫生组织淋巴肿瘤分类将其与原发性睾丸大B细胞淋巴瘤和原发性玻璃体视网膜淋巴瘤(primary vitreoretinal lymphoma,PVSL)统称为免疫豁免部位原发性大B细胞淋巴瘤(primary large B-cell lymphoma of immune-privileged sites,IP-LBCL),此类肿瘤具有相似的免疫表型与分子特征,且对特定解剖部位具有高度选择性[2-3]。国际共识分类将其归类于活化B细胞样(activated B-cell-like,ABC)亚型的结外弥漫大B细胞淋巴瘤(diffuse large B-cell lymphoma,DLBCL),大多数为MCD/C5/MYD88基因组亚型[4]。PCNSL的中位发病年龄为65岁,既往人类免疫缺陷病毒感染人群发病率较高,而随着人口老龄化进程加快,免疫功能正常人群的发病率呈逐年上升趋势,尤以70岁以上老年群体更为显著[5-7]。

尽管PCNSL对放化疗具有一定的敏感性,但其预后差于系统性DLBCL,PCNSL的5年总生存率为30%~40%,而接受标准治疗后DLBCL的5年总生存

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率约为70%[8]。这一差异的核心原因在于常规治疗药物难以穿透血脑屏障(blood-brain barrier,BBB),治疗药物选择受限。目前,以大剂量甲氨蝶呤(high-dose methotrexate,HD-MTX)为基础的联合方案是PCNSL的一线诱导方案,序贯自体造血干细胞移植(autologous stem cell transplantation,ASCT)为主要巩固治疗手段[9-10]。然而,由于PCNSL患者发病年龄偏高,多数患者因体能状态差或并发症无法耐受ASCT治疗。此外,高复发率、HD-MTX相关脏器毒性以及联合治疗方案的选择,仍是当前临床亟待突破的瓶颈。全脑放疗(whole-brain radiotherapy,WBRT)虽可作为巩固治疗选择,但即便是低剂量放疗也存在诱发严重迟发性神经毒性的风险,因此临床多将ASCT作为首选巩固方案[11-12]。诱导化疗方案中,含HD-MTX的联合方案(联用可穿透BBB的化疗药物)完全缓解(complete response,CR)率为24%~63%,三药甚至四药联合的方案优于单药治疗[13]。

基因和转录组测序研究[14]结果表明,PCNSL的核心发病机制为B细胞受体(B-cell receptor,BCR)或Toll样受体(Toll-like receptor,TLR)通路的突变,这些突变会导致核因子κB(nuclear factor κB,NF-κB)的激活,抑制终末B细胞分化和凋亡。PCNSL中BCR/TLR/ NF-κB信号的激活依赖于多种遗传学改变,其中以*CD79B*和(或)*MYD88*的突变最为常见[15]。基于PCNSL独特的生物学特性及治疗药物需穿透BBB的要求,布鲁顿酪氨酸激酶抑制剂(Bruton's tyrosine kinase inhibitor,BTKi)成为其精准治疗的重要方向。布鲁顿酪氨酸激酶(Bruton's tyrosine kinase,BTK)是B细胞增殖和分化的关键调控分子,活化的BTK可介导BCR和TLR信号向下游NF-κB通路传导。MYD88是TLR信号通路中的关键衔接分子,可通过形成MYD88-IRAK复合物激活NF-κB通路[14]。CD79B可以激活下游NF-κB信号通路,*CD79B*突变抑制BCR信号通路的负向调控,导致NF-κB信号通路的慢性激活[16]。BTKi可逆或者不可逆地结合BTK,抑制BTK活性而发挥抗肿瘤效应[17]。同时,作为小分子靶向药物,多项研究[18-19]证实多种BTKi能够透过BBB,在脑脊液中达到有效治疗浓度。

目前,全球共获批6种BTKi,依据作用机制与研发代次分为3代:第一代药物为伊布替尼;第二代药物为泽布替尼、阿可替尼、奥布替尼、替拉鲁替尼;第三代药物为匹妥布替尼。除了替拉鲁替尼,其他药物均在中国上市,获批适应证包括慢性淋巴细胞白血病/小淋巴细胞淋巴瘤、华氏巨球蛋白血症、套细胞淋巴瘤、边缘区淋巴瘤等,但BTKi药物尚未在国内获批PCNSL治疗适应证。尽管如此,越来越多的临床数据表明,BTKi药物在PCNSL治疗中获得了较好的疗效,本文将围绕目前的临床试验数据进行阐述。

1　第一代BTKi

伊布替尼是首个共价结合的BTKi,通过不可逆结合BTK活性位点Cys-481阻断NF-κB通路,是首个证实对PCNSL安全有效的BTKi药物[16]。1项针对复发难治(recurrent/refractory,R/R)PCNSL患者的Ⅰ/Ⅱ期剂量递增研究[20]显示,伊布替尼(560~840 mg/d)治疗的13例患者中,10例获得客观缓解,包括5例CR和5例部分缓解(partial remission,PR),中位无进展生存期(progression free survival,PFS)为4.6个月。另一项Ⅱ期研究伊布替尼单药(560 mg/d)治疗R/R PCNSL或PVSL患者,客观缓解率(objective response rate,ORR)为52%,CR率为19%,中位PFS为4.8个月,中位总生存期(overall survival,OS)为19.2个月[21]。

为克服单药治疗缓解持续时间较短的缺陷,多项研究探索了伊布替尼联合治疗方案。1项Ⅰb期研究采用利妥昔单抗+HD-MTX+伊布替尼治疗R/R PCNSL患者,ORR为80%,CR率为53%,中位PFS为9.2个月[22]。另一项Ⅰb期研究先给予伊布替尼单药诱导,再序贯伊布替尼联合利妥昔单抗、脂质体霉素、替莫唑胺、依托泊苷和地塞米松(DA-TEDDi-R)方案,治疗后患者CR率为86%,ORR为94%,中位PFS为15.3个月,但需注意该方案会使曲霉病发生率升高至39%[16]。1项Ⅱ期研究优化了治疗策略,先给予2周伊布替尼单药治疗,对伊布替尼敏感者采用TEDDi-R方案,耐药者采用TEDD-R方案,同时给予艾沙康唑预防真菌感染,结果显示,57%的患者伊布替尼治疗有效;TEDDi-R的ORR为92%,CR率为77%,TEDD-R的ORR为45%,CR率为28%,且未发生机会性感染[23]。

对于新诊断(new diagnosis,ND)PCNSL患者,伊布替尼同样展现出良好疗效。1项Ⅱ期的单中心研

究评估了伊布替尼联合利妥昔单抗、HD-MTX、甲基苄肼和长春新碱（R-MVPi）的疗效，30例患者中有29例达到CR，1例达到PR，后续19例接受了阿糖胞苷巩固治疗，8例接受ASCT，2年PFS为84.2%[24]。另一项多中心Ⅱ期临床研究采用伊布替尼联合HD-MTX及替莫唑胺方案，ORR为93.9%，CR率为72.7%，2年PFS和OS分别为57.6和84.8%，≥3级不良事件发生率仅为27.3%[25]。

虽然伊布替尼与BTK共价结合，但它也结合其他激酶，包括TEC激酶家族中的ITK、EGFR、JAK3和HER2。这也是其治疗相关毒性的主要原因，常见不良反应包括心律失常、感染和出血[26]。

2　第二代BTKi

第二代BTKi同样通过与Cys-481位点不可逆结合发挥作用，但对BTK靶点具有更高选择性，显著降低脱靶效应[27]。尤为重要的是，第二代药物的心血管不良事件发生率相对更低，在合并高血压、心房颤动等心血管疾病史的患者中更具优势[28]。

替拉鲁替尼是目前唯一获批PCNSL适应证的BTKi，于日本上市用于治疗R/R PCNSL患者。1项Ⅰ/Ⅱ期临床试验中，替拉鲁替尼单药治疗R/R PCNSL患者44例，ORR为64%，中位PFS为2.9个月[29]；3年随访数据提示，患者3年PFS率和OS率分别为13.9%和56.7%，长期治疗的患者在Karnofsk功能状态评分和生活质量评分均维持在较高水平，提示部分患者可获得持久深度缓解[30]。上市后真实世界研究[31]纳入189例R/R PCNSL患者，ORR为61.2%，≥3级的不良反应约24.3%。目前，替拉鲁替尼在ND PCNSL及联合治疗领域仍缺乏前瞻性研究。

研究[19]证实泽布替尼可有效穿透BBB并发挥抗PCNSL作用。1项前瞻性、多中心研究[32]采用泽布替尼联合来那度胺、利妥昔单抗、替莫唑胺和甲氨蝶呤（RLZT ± MTX）方案治疗ND PCNSL，24例患者ORR为79.2%，CR率为37.5%。另一项前瞻性研究[33]采用泽布替尼联合利妥昔单抗、甲氨蝶呤（R-MZ）方案，29例初治患者ORR和CR率均达到89.7%，且安全性可控。多中心真实世界研究[34]进一步验证了R-MZ方案的疗效，35例初治患者CR率为80%，ORR为88.6%；亚组分析显示，接受泽布替尼维持治疗或ASCT巩固治疗组的PFS明显优于停药观察组（22个月 vs. 未达到，$P = 0.012$）。

奥布替尼是我国自主研发的第二代BTKi。1项单中心Ⅱ期研究[35]采用奥布替尼联合利妥昔单抗及HD-MTX（ORM）治疗初治PCNSL，28例患者ORR为71.4%，CR率57.1%，中位PFS为35.3个月。后续1项多中心Ⅱ期研究[36]进一步证实，ORM方案诱导治疗的ORR达90.3%，CR率为87.1%。1项回顾性研究[37]比较奥布替尼单药与伊布替尼单药治疗R/R PCNSL，奥布替尼的ORR和PFS均优于伊布替尼。

目前阿可替尼的相关研究数据较少，有病例报道[38]显示，阿可替尼用于R/R PCNSL患者的巩固和维持治疗，随访18个月患者仍处于CR状态。1项Ⅰ期的临床研究[39]应用阿可替尼联合度伐利尤单抗治疗R/R PCNSL，ORR和CR率均为40%。

3　第三代BTKi

匹妥布替尼是一种强效、非共价（可逆）结合的高选择性BTKi，其作用机制不依赖Cys-481位点，可有效克服一、二代药物因Cys-481突变产生的耐药问题[40]。尽管目前该药在PCNSL领域的临床数据尚属空白，但其独特的作用机制为耐药患者的治疗提供了新方向，具有较高的研究价值与应用潜力。

4　结语

综上所述，PCNSL作为高度侵袭性淋巴瘤，传统以HD-MTX为基础的治疗方案面临毒性大、复发率高等挑战。基于PCNSL中高频率出现*MYD88*和*CD79B*基因突变及其对BCR/TLR/NF-κB信号通路的依赖性，BTKi的应用为其治疗开辟了精准靶向的新路径。第一代药物伊布替尼率先证实了BTKi治疗PCNSL的有效性，但其脱靶效应限制了其临床应用；以替拉鲁替尼、泽布替尼和奥布替尼为代表的第二代药物，在保持BBB穿透能力的同时，表现出更高的靶点选择性，改善了心血管安全性和整体耐受性。目前的临床研究证实，BTKi单药治疗虽然有效率较高，但缓解持续时间有限；联合治疗方案在提高ORR和PFS上有显著优势，但仍需扩大临床样本量并且延长观察时间以全面评价长期疗效和安全性。第三代非共价结合BTKi匹妥布替尼在克服耐药方面展现出独特优势，但其BBB穿透能力与PCNSL的疗效方面仍需前瞻性研究验证。随着更多大规模多

中心随机对照研究的开展，基于BTKi的联合治疗方案有望成为PCNSL标准化治疗的核心组成部分。未来研究应聚焦于明确BTKi在诱导治疗中的最佳组合方式，及其在维持治疗中的最佳剂量与疗程，进一步优化PCNSL的治疗策略。

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