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乳腺癌脑转移的药物治疗最新进展*

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摘要: 随着治疗的进步,晚期乳腺癌患者的生存时间得到了明显延长,但患者发生中枢神经系统转移的概率也随之升高。尽管手术和放疗等局部治疗方法仍是脑转移治疗的主要手段,但药物治疗脑转移已经成为近年来研究关注的重点,特别是抗人表皮生长因子受体-2(HER2)药物,如小分子酪氨酸激酶抑制剂等,已经在HER2阳性乳腺癌脑转移的治疗中显示了较好疗效。此外,一些研究也显示,作用于其他靶点的药物,如抗血管生成药物、PARP抑制剂、免疫检查点抑制剂等,对脑转移也有一定疗效。

关键词: 乳腺癌; 脑转移; 化疗; 靶向治疗; 免疫治疗

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Drug treatment advances for brain metastases of breast cancer*

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Abstract: With the progress of treatment, the survival time of patients with advanced breast cancer has been significantly extended, but the probability of central nervous system metastases in patients is also increased. Although local treatments such as surgery and radiation therapy are still the main means of brain metastases treatment, drug treatment of brain metastases has become the focus of research in recent years. In particular, anti-human epidermal growth factor receptor 2(HER2) drugs, such as small-molecule tyrosine kinase inhibitors, have shown good efficacy in the drug treatment of HER2-positive brain metastatic breast cancer. In addition, some studies have also shown that drugs acting on other targets, such as anti-angiogenic drugs, PARP inhibitors, and immune checkpoint inhibitors, also have a certain effect on brain metastases.

Keywords: Breast cancer; Brain metastasis; Chemotherapy; Targeted therapy; Immunotherapy

0 前言

世界卫生组织国际癌症研究机构(International Agency for Research on Cancer, IARC)发布了2020年全球最新癌症负担数据,乳腺癌取代肺癌,成为全球第一大癌。随着对乳腺癌分子生物学认识的深入和治疗水平的不断提高,早期乳腺癌患者5年生存率超过90%,但脑转移的发生率也随之上升^[1]。由于脑部的特殊解剖结构,脑转移与乳腺癌常见转

移部位骨、肺、肝等不同。放疗一直是脑转移治疗的主要手段,但是其剂量和次数是有限的,并且放疗后脑内病灶再次进展、相关并发症及患者生存质量下降等问题仍然亟待解决^[2]。在此情况下,如何通过药物治疗乳腺癌脑转移已经成为当下的热点话题。本文通过对乳腺癌脑转移的药物治疗最新进展进行综述,旨在为临床通过药物治疗乳腺癌脑转移提供参考。

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1 脑部独特的微环境导致脑转移的独特性

早在 120 年前, Steven Paget 教授就提出了“种子-土壤”学说, 转移的肿瘤细胞就是种子, 转移器官微环境就是土壤^[3], 但我们对于大脑内肿瘤微环境的了解相对较少。中枢神经系统(central nervous system, CNS)最独特的特征是血脑屏障(blood-brain barrier, BBB)。BBB 是脑微血管内皮细胞的选择性扩散屏障, 给 CNS 的转移和渗透造成了重大障碍^[4]。CNS 渗透乳腺癌脑转移的关键介质包括环氧合酶 2(cyclooxygenase 2, COX2)、表皮生长因子

受体(epidermal growth factor receptor, EGFR)配体 HBEGF、 $\alpha 2, 6$ -唾液酸转移酶 ST6GALNAC5 和特定的基质金属蛋白酶(matrix metalloproteinase, MMP)等^[5-6]。肿瘤细胞穿过 BBB 进入脑内, 必然要和脑内的“原住民”星形胶质细胞、小神经胶质细胞、神经元等争夺空间。在这个过程中, 不同的信号通路被激活, 如 Wnt、Notch、MAPK、c-Met、NMDARs 等(图 1)^[7]。转移肿瘤细胞进入脑内并生存的过程非常复杂, 还有很多未解之谜, 这既为我们的临床治疗提供了思路, 也带来了挑战^[8-9]。

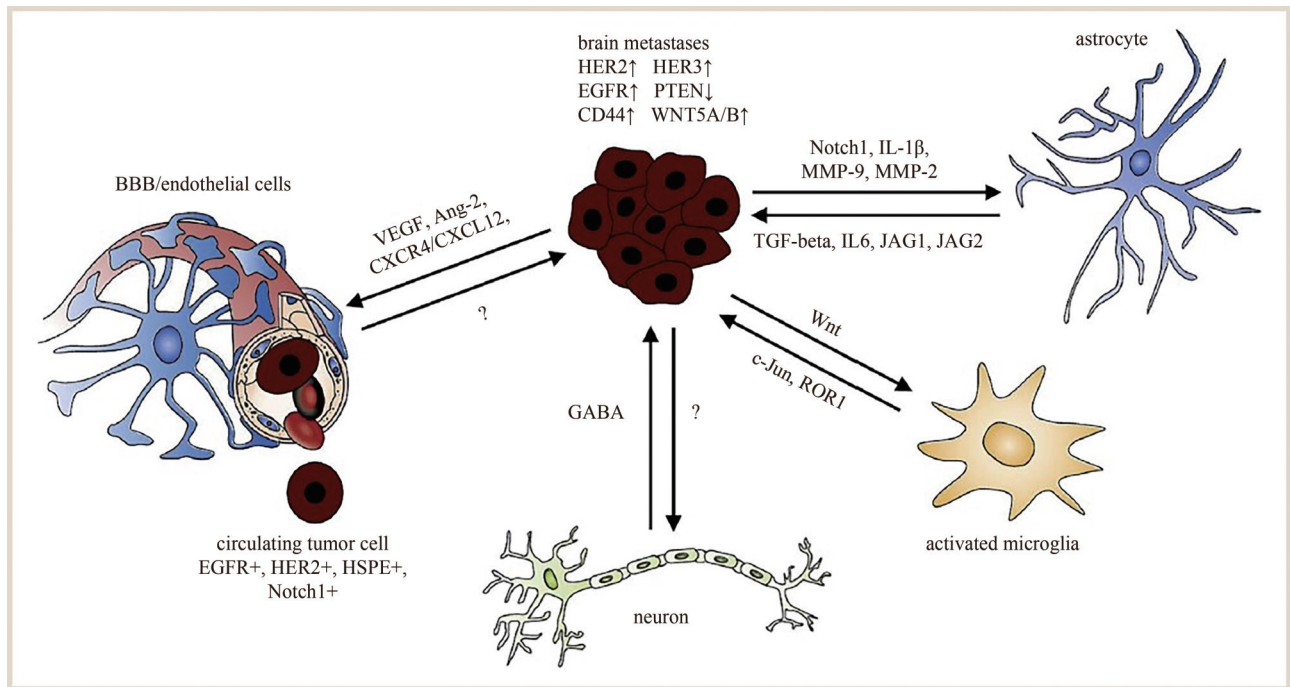


图 1 乳腺癌脑转移的图解^[7-8]

Fig. 1 The illustration of breast cancer brain metastases

2 传统化疗药物治疗乳腺癌脑转移疗效不确定

近些年, 乳腺癌患者的生存得到明显改善, 化疗在其中起到了重要作用。但是, 由于化疗药物分子量较大, 携带电荷, 并且容易与白蛋白结合, BBB 渗透性不佳, 故单一化疗方案在脑转移中的疗效一般^[10]。目前有许多正在进行的研究旨在克服 BBB 的障碍。有研究显示, Angiopep-2 可与紫杉醇共价连接(ANG1005), 利用低密度脂蛋白受体相关蛋白 1(low density lipoprotein receptor-related protein-1, LRP-1)穿过 BBB^[11]。目前有很多肽-药物偶联物正在进行临床试验, 如 NCT03613181、

NCT02915744 等^[4, 12], 但使用传统化疗药物治疗脑转移, 显然已不是主流。

3 单克隆抗体类药物治疗脑转移有一定疗效

人表皮生长因子受体-2(human epidermal growth factor receptor 2, HER2)阳性乳腺癌占全部乳腺癌患者的 20%~30%, 是一类以侵袭性强著称的乳腺癌。如果 HER2 阳性乳腺癌患者未接受抗 HER2 治疗, 其复发转移风险是 HER2 阴性患者的 2~3 倍。临床中, 随着抗 HER2 治疗的广泛应用, HER2 阳性乳腺癌患者 OS 明显延长, 但是高达 50% 的患者会在其病程中发生脑转移。因此, 针对

HER2 阳性乳腺癌脑转移的治疗是目前研究的重点^[13-14]。抗 HER2 治疗药物主要有抗体类药物(曲妥珠单抗、帕妥珠单抗)、小分子酪氨酸激酶抑制剂(tyrosine kinase inhibitor, TKI)(拉帕替尼、奈拉替尼、吡咯替尼、图卡替尼、阿法替尼)和抗体药物偶联物(antibody-drug conjugate, ADC)(T-DM1、DS-8201)。

曲妥珠单抗和帕妥珠单抗是分别靶向 HER2 受体胞外二聚化结构域 IV 区和 II 区的单克隆抗体。III 期 CLEOPATRA 研究的回顾性探索分析显示,联用帕妥珠单抗可延迟 CNS 作为疾病进展首发部位的中位时间^[15]。PHEREXA 研究中,脑转移亚组使用曲妥珠单抗和帕妥珠单抗双靶联合卡培他滨,显示出无进展生存期(progression-free survival, PFS)获益的趋势^[16]。但一项单臂、前瞻性、II 期研究中,采用高剂量曲妥珠单抗(每周 6 mg·kg⁻¹)和帕妥珠单抗联合化疗治疗脑转移,包括放疗后再次进展的脑转移患者,CNS 客观缓解率(objective response rate, ORR)仅为 11%^[17],疗效并不显著。

4 小分子 TKIs 治疗脑转移疗效确定

TKIs 由于分子量小,更易穿透 BBB,成为脑转移治疗的希望所在。拉帕替尼(lapatinib)是靶向 HER2、EGFR 且可以穿过 BBB 的多靶点小分子 TKI。最早为患者带来药物治疗乳腺癌脑转移希望的是 LANSCAPE 研究。该研究发现,拉帕替尼联合卡培他滨治疗未经放疗的脑转移患者,颅内病灶有效率达 57.1%,使患者接受全脑放疗的时间推迟了 8.3 个月,并且先进行药物治疗后再进行全脑放疗,患者仍然有 17 个月的总生存期(overall survival, OS)^[18]。该方案在当年获得了美国临床肿瘤学会(American Society of Clinical Oncology, ASCO)乳腺癌脑转移治疗指南推荐,并说明对于有限转移灶无症状的 HER2 阳性乳腺癌脑转移患者可以先行药物治疗。随着更多抗 HER2 小分子 TKIs 问世,关于 TKIs 治疗脑转移的相关研究也逐渐增多。

奈拉替尼(neratinib)是靶向 HER1、HER2 和 HER4 的多靶点小分子 TKI。一项针对脑转移患者的 II 期临床研究(TBCRC022)分别纳入拉帕替尼初治(3A,共 39 例)和拉帕替尼治疗(3B,共 12 例)乳腺癌脑转移患者^[19]。3A 组患者 CNS 缓解率为 49%(95% CI: 32%~66%),3B 组患者 CNS 缓解率为 33%(95% CI: 10%~65%),两组中位 PFS 分别为

5.5 个月(3A)和 3.1 个月(3B),中位 OS 分别为 13.3 个月(3A)和 15.1 个月(3B)。此外在 NALA 研究、NEFERT-T 研究中,也入组了少量无症状脑转移患者,并观察到约 20% 的颅内病灶有效率^[20-21]。基于现有研究,2019 年美国食品药品监督管理局(U.S. Food and Drug Administration, FDA)授予奈拉替尼作为治疗乳腺癌脑转移的孤儿药资格。

阿法替尼(afatinib)是靶向 EGFR 和 HER4 的新型 TKI。一项比较阿法替尼单药、阿法替尼联合长春瑞滨以及研究者选择的治疗方案对 HER2 阳性乳腺癌脑转移患者的疗效与安全性的 II 期临床研究[LUX-Breast3(NCT01441596)]结果显示,阿法替尼组患者生存获益并没有明显提升,反而增加了不良事件的发生。因此,该研究未能显示出阿法替尼用于乳腺癌脑转移患者治疗的任何益处^[4, 22-23],阿法替尼在乳腺癌脑转移中的作用仍需进一步研究。未来在使用阿法替尼之前,可能需要评估患者中除 HER2 之外的 EGFR 的表达情况,以更好地了解该药物和其他类似靶向药物在乳腺癌脑转移中的潜在作用。

近两年,新的抗 HER2 药物不断涌现,特异性靶向 HER2 基因的小分子 TKI 图卡替尼(tucatinib)在脑转移治疗中显示了较好疗效。在 HER2CLIMB 研究中,总计有 291 例脑转移患者入组,图卡替尼组颅内病灶的 PFS 从 4.2 个月延长到 9.9 个月($HR=0.32$, $P<0.000\ 01$),OS 从 12.0 个月延长到 18.1 个月,图卡替尼也成为首次在随机对照研究中被证实可以延长 HER2 阳性晚期脑转移患者 OS 的 TKI^[14]。

我国自主研发的小分子 TKI 吡咯替尼(pyrotinib),是靶向 HER1/HER2/HER4 的不可逆强效 TKI。PHENIX 临床研究入组了 10% 左右无症状脑转移患者,研究结果显示,对于脑转移患者,吡咯替尼联合卡培他滨的 PFS 可达 6.9 个月,表明吡咯替尼治疗脑转移有一定疗效^[24]。在一项真实世界研究中发现,吡咯替尼在脑转移患者中的 PFS 为 8.8 个月,显著改善了患者的预后^[25]。PERMEATE 研究是一项单臂、前瞻性、II 期研究,采用吡咯替尼联合卡培他滨治疗放疗后进展的脑转移患者,CNS ORR 为 42.1%,PFS 为 5.6 个月;治疗未经放疗的脑转移患者,CNS ORR 为 74.6%,PFS 为 11.3 个月,与颅外病灶治疗效果相当^[26],说明吡咯替尼可作为既往未经 TKIs 治疗、局部症状可控的活动性脑转移系统治疗的优选方案。

在晚期乳腺癌脑转移的药物治疗研究中,目前显示出较好临床应用前景的药物是抗 HER2 的小分子 TKIs,但是药物仍然比较有限,如何应用、何时应用、联合应用还是单药应用、对脑膜转移疗效如何,都还是未知数,需要进一步研究。

5 ADC 类药物治疗脑转移显示一定效果

Trastuzumab emtansine (T-DM1) 是一种新型 ADC,其中 emtansine 可与曲妥珠单抗稳定地结合^[27-28]。EMILIA 试验的 991 例患者中有 95 例在注册时出现了 CNS 转移,对这 95 例患者进行回顾性探索分析,分析结果显示,使用 T-DM1 治疗的患者 OS 有显著改善(26.8 个月 vs. 12.9 个月)^[23, 29-30]。KAMILLA (NCT01702571) 是一项正在进行的 IIIb 期 T-DM1 研究,共纳入 2 002 例患者,其中有 398 例患者基线确诊脑转移。在 126 例可测量病灶的脑转移患者中,最佳总缓解率和临床获益率分别为 21.4% (95% CI: 14.6% ~ 29.6%) 和 42.9% (95% CI: 34.1% ~ 52.2%),中位 PFS 为 5.5 个月(95% CI: 5.3 ~ 5.6),OS 也达到了 18.9 个月(95% CI: 17.1 ~ 21.3)。这一前瞻性研究结果表明了 T-DM1 在 HER2 阳性脑转移患者中的应用潜力^[31]。

Trastuzumab deruxtecan (T-DXd) 是由抗 HER2 抗体、可切割四肽连接物和细胞毒性拓扑异构酶 I 抑制剂组成的 ADC,旨在改善目前可用的抗体结合物的关键属性,较 T-DM1 具有更高的药物抗体比,同时保持良好的药代动力学特征,在脑转移患者中也取得了优异疗效。DESTINY-Breast01 研究共纳入 524 例不可切除或转移性 HER2 阳性乳腺癌患者,其中包括 82 例基线有脑转移的患者。2021 年圣安东尼奥乳腺癌研讨大会(San Antonio Breast Cancer Symposium, SABCS)报道了该研究的亚组分析结果:对于伴有脑转移的患者,T-DXd 组和 T-DM1 组中位 PFS 分别为 15 个月和 3 个月,两组颅内 ORR 分别为 67.4% 和 20.5%^[32]。T-DXd 对脑转移患者也有较好疗效,为未来脑转移患者的治疗带来了新的希望。

6 特殊靶点药物治疗脑转移的进展

晚期三阴性乳腺癌患者发生脑转移的比例也接近 50%,研究发现携带 BRCA 基因突变的患者有更高的脑转移风险,脑转移患者 BRCA 突变比例亦较高^[33-34]。奥拉帕利(olaparib)是首个靶向抑制

DNA 损伤修复酶的口服多腺苷二磷酸核糖聚合酶[poly(ADP-ribose) polymerase, PARP]抑制剂。在 OlympiAD 研究中,对于有胚系 BRCA 突变的患者,奥拉帕利单药与医生选择的化疗方案相比,中位 PFS (7 个月 vs. 4.2 个月; HR=0.58, 95% CI: 0.43 ~ -0.80; P=0.000 9)显著延长^[35]。临床指南已经推荐针对晚期乳腺癌并伴有胚系 BRCA 突变的患者优先选择奥拉帕利治疗,目前也有研究探讨其在伴有 BRCA 基因突变脑转移患者中的治疗价值^[36]。

Veliparib 是一种可以通过 BBB 的口服 PARP 抑制剂,在一项纳入 25 例乳腺癌脑转移和脑部受累患者的 I 期临床试验中,乳腺癌脑转移患者的 6 个月生存率为 61% (95% CI: 39% ~ 78%),颅内 ORR 为 41%^[37]。正在进行的 II 期试验(NCT02595905)中,对转移性乳腺癌患者在给予顺铂治疗的基础上随机采用 Veliparib 或安慰剂治疗,期待该项研究带来好的结果。未来还需要在乳腺癌脑转移患者中进一步探索 PARP 抑制剂的疗效与安全性^[4]。

贝伐珠单抗(bevacizumab)是一种血管内皮生长因子(vascular endothelial growth factor, VEGF)抑制剂。近年来,贝伐珠单抗在治疗乳腺癌脑转移方面已显示出潜力。在一项单臂 II 期研究中,使用贝伐珠单抗、依托泊苷和顺铂治疗的 35 例乳腺癌脑转移患者中,27 例(77.1%)具有 CNS 客观反应,其中包括 13 例 CNS 转移体积减少 $\geq 80\%$ 的患者。但这一反应很可能是由于颅内肿瘤周围水肿减轻引起,药物治疗是否有效还待考量^[38]。目前还需要进行更多的研究来确定贝伐珠单抗与化疗药物的最佳组合和顺序并对其疗效进行评价。

细胞周期蛋白 D-CDK4/6-INK4-Rb 通路可调节细胞有丝分裂从 G₁ 期(DNA 合成前)到 S 期(合成)的过渡^[39],此步骤对于控制细胞增殖至关重要,在几种恶性肿瘤中均可见该途径的失调^[40]。因此,靶向该通路的药物——周期蛋白依赖性激酶 4/6 (cyclin-dependent kinases 4/6, CDK4/6)抑制剂应运而生,这一类药物主要有 3 种:哌柏西利(palbociclib)、阿贝西利(abemaciclib)和瑞波西利(ribociclib)。近年来,几项大型前瞻性试验(MONARCH 2^[41]、PALOMA-3^[42]、MONARCH-3^[43]、PALOMA-2^[44]和 MONALEESA-7^[45]等)表明,CDK4/6 抑制剂治疗 HR 阳性晚期乳腺癌疗效明确。阿贝西利已经开展了单药治疗乳腺癌、非小细胞肺癌、黑色素瘤脑转移患者的 II 期研究,研究显示颅内病灶控制率可达到

66%^[46-47]。考虑到 CDK4/6 抑制剂对乳腺癌脑转移的潜在疗效,目前正在进行多项前瞻性研究,评价其在乳腺癌脑转移中的疗效及安全性,如用来评估阿贝西利(NCT02308020)和哌柏西利(NCT02774681)疗效的两项研究^[48]。其中 NCT02308020 的早期结果以摘要形式发表,研究发现,在接受大量预处理的患者中使用阿贝西利治疗的颅内临床获益率为 25%,中位 PFS 为 4.4 个月^[4]。未来希望能有更多的研究结果问世,给脑转移患者提供更多的治疗选择。

PIK3/AKT/mTOR 途径是转移性乳腺癌最常见的基因组突变之一。针对 mTOR 这一途径的新型靶向药物依维莫司(everolimus)与芳香化酶抑制剂的联合使用已在绝经后激素受体阳性转移性乳腺癌中显示出显著疗效^[49]。在一项针对室管膜下巨细胞星形细胞瘤患者的 III 期试验(NCT00789828)中,结果显示依维莫司可导致肿瘤缩小 50%,据此可推断依维莫司是有 CNS 活性的^[50]。最近的体外研究表明,pan-Akt 抑制剂具有穿越 BBB、降低肿瘤细胞活力并诱导脑转移瘤凋亡的能力^[51]。这些药物的研究还处于早期的探索阶段,也期待能有好的结果。

7 免疫检查点抑制剂治疗脑转移的探索

大脑很长时间以来一直被认为是具有免疫特权的器官,但免疫检查点抑制剂在脑转移治疗中的疗效已经在黑色素瘤脑转移患者中显现。2012 年 *Lancet Oncology* 杂志发表的前瞻性 II 期研究结果证实伊匹木单抗(ipilimumab)治疗脑转移有效^[52];后续多项研究表明,免疫检查点抑制剂在黑色素瘤和非小细胞肺癌的脑转移中有显著疗效^[4, 53]。乳腺癌虽然是免疫检查点抑制剂攻城略地的最后堡垒,但最近几年,在三阴性乳腺癌的新辅助治疗和晚期治疗中,程序性死亡受体 1(programmed death-1, PD-1)和程序性死亡受体配体 1(programmed death-ligand 1, PD-L1)抑制剂联合化疗均取得了较单药化疗有效的结果^[54-55]。尽管 IMpassion130 的亚组分析显示 PD-L1 抑制剂阿替利珠单抗(atezolizumab)在脑转移亚组没有获益趋势^[56],但有许多临床试验正在探索放疗与阿替利珠单抗(NCT03483012)、纳武利尤单抗(NCT03807765)、帕博利珠单抗(NCT03449238)联合治疗乳腺癌脑转移的疗效^[4, 57],未来期待更多有关免疫检查点抑制剂治疗乳腺癌脑转移的临床

研究结果问世。

8 总结

在过去的几十年中,尽管乳腺癌脑转移的治疗取得了长足进步,但仍需不断努力来改善患者的临床预后。目前的研究关注点是与脑转移发生发展信号通路相关的靶向治疗,可以说靶向治疗是脑转移治疗的未来。乳腺癌脑转移患者要获得成功治疗并延长生存期,最终仍需要包括神经外科、放疗科、肿瘤内科等多学科的参与,共同提高患者的治疗管理水平。

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