·综　述·

激素受体阳性乳腺癌化疗同期内分泌治疗的研究进展

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摘要：化疗和内分泌治疗是激素受体(HR)阳性人表皮生长因子受体 2 (HER2)阴性乳腺癌全身治疗的重要组成部分,可显著改善患者预后。基于早期的循证医学证据,国内外指南推荐乳腺癌化疗序贯内分泌治疗而非同期。但是,随着对肿瘤生物学行为的理解加深、新药物的研制、治疗方式的更新,同期治疗或许有其独特的治疗优势,也再次引起了学者们的兴趣。本文将从基础研究和临床研究(包括晚期解救治疗、局部晚期新辅助治疗及早期辅助治疗)两方面对 HR 阳性 HER2 阴性乳腺癌化疗同期内分泌治疗的最新进展及适用时机进行综述。

关键词：乳腺癌；激素受体阳性；化疗同期内分泌治疗；人表皮生长因子受体 2；新辅助治疗；芳香化酶抑制剂

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Research progress of hormone receptor positive breast cancer chemotherapy combined with endocrine therapy

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Abstract: Chemotherapy and endocrine therapy are important components of systemic therapy for hormone receptor (HR)-positive human epidermal growth factor receptor 2 (HER2)-negative breast cancer, which can significantly improve the prognosis of patients. Based on early evidence-based medical evidence, domestic and foreign guidelines recommend sequential endocrine therapy rather than concurrent chemotherapy for breast cancer. However, with the deepening of the understanding of tumor biological behavior, the development of new drugs, and the updating of treatment methods, concurrent treatment may have its unique therapeutic advantages, which has once again aroused the interest of scholars. This article will review the latest progress and applicable time of endocrine therapy in the chemotherapy of HR positive HER2 negative breast cancer from two aspects of basic research and clinical research (including late rescue therapy, locally advanced neoadjuvant therapy and early adjuvant therapy).

Keywords: Breast cancer; Hormone receptor positive; Chemotherapy combined with endocrine therapy; Human epidermal growth factor receptor 2; Neoadjuvant therapy; Aromatase inhibitor

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乳腺癌是全球女性最常见的癌症,也是女性癌症死亡的主要原因。2020 年全球新确诊女性乳腺癌病例约 226 万,死亡人数约 68 万,成为影响女性健康的主要威胁之一[1]。分子分型为激素受体(hormone receptor, HR)阳性人表皮生长因子受体 2 (human epidermal growth factor receptor2, HER2)阴性最为常见,约占全球乳腺癌患者的 75%[2]。化疗和内分泌治疗在 HR 阳性 HER2 阴性乳腺癌的治疗中具有重要地位,传统观念并不支持化疗同期内分泌治疗[3]。但是最新的研究对该观点产生了巨大的冲击。本文将从基础研究及临床试验两个方面对 HR 阳性 HER2 阴性乳腺癌化疗同期内分泌治疗的最新进展进行综述。

1　基础研究

研究表明组蛋白 H3 激酶抑制剂可增强紫杉醇的抗癌功效[4-5],而在携带 ZNF423 突变基因的 HR 阳性 ZR751 细胞株中,他莫昔芬(tamoxifen, TAM)通过影响 ZNF423 抑制组蛋白 H3 激酶编码因子 VRK1 和 PBK 表达而提高细胞的化疗敏感性[6]。

作为新型抗雌激素药物的芳香化酶抑制剂(aromatase inhibitor, AI)通过阻断雄激素的芳香化过程而抑制雌激素产

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生,发挥抗雌激素作用。目前应用于临床的主要是阿那曲唑、来曲唑和依西美坦。替吉奥(S-1) 处理 MCF-7 细胞株及肿瘤异种移植小鼠 (BALC/c nu/nu)后,雌激素受体 α(estrogen receptor α,ERα)高表达细胞的比例及 ERα 表达水平下降,进而抑制 ERα 通路诱导的细胞生长,增强阿那曲唑的抗癌作用[7-8]。近期研究表明低剂量节拍化疗协同依西美坦抑制 PI3K 表达,促进 AKT 蛋白及下游通路信号蛋白磷酸化水平升高,从而激活凋亡信号,抑制 MCF-7 细胞增殖[9]。

大量体内外实验发现雌激素可促进化疗耐药因子 BCL-2 及 MAPT 表达升高,另 ERα 与连接到 MDR1 启动子上的特异蛋白转录因子 1(specific protein transcription factor 1,Sp1)相互作用,激活 MDR1 转录,降低化疗敏感性[10-13],而氟维司群(fulvestrant, FUL)作为选择性雌激素受体下调剂(selective estrogen receptor degrader, SERD),可结合并降解 ERα,逆转 ER 通路介导的化疗耐药;另外,S-1 促进 FUL 降解 ERα [14],显示了化疗同期内分泌治疗的潜在优势。

2　临床研究

2.1　*HR 阳性晚期乳腺癌解救治疗*　晚期乳腺癌是临床实践的难点。内分泌治疗是 HR 阳性晚期乳腺癌主要的治疗手段。有限的敏感性及严重的不良反应限制了常规化疗在该类型乳腺癌中的应用,而节拍化疗作为一种低剂量、有或无治疗停顿的给药方案,毒性小,治疗相关不良事件发生率低,患者依从性更高[15]。多项对比节拍化疗同期内分泌治疗和单化疗、单内分泌治疗疗效的临床前研究表明同期方案抗癌疗效显著增加[8]。越来越多的回顾性研究及临床试验也有力例证了同期治疗的可行性。

一项以评估卡培他滨同期 AI 作为 HR 阳性晚期女性乳腺癌一线治疗的安全性及有效性为目的的回顾性研究显示,中位随访 47 个月时,同期组中位无进展生存期(progression free survival, PFS)及总生存期(overall survival, OS)明显长于单 AI 组(PFS:同期组 22 个月,单 AI 组 14 个月,$P=0.002$;OS:同期组 66 个月,单 AI 组 49 个月,$P=0.000\ 3$)。特别是 ER 低表达、内脏转移、既往接受过 AI 治疗和无病间隔期长的人群在同期治疗中获益更明显[16-17]。

另一项二期临床试验纳入了绝经后 HR 阳性晚期乳腺癌患者,以探索卡培他滨节拍化疗同期第三代 AI 安全性和耐受性,在平均随访 14.8 个月时,客观缓解率达到 70.5%,中位 PFS 为 16.2 个月,4 例患者出现 3 级毒症(手足综合征),其他不良事件均未超过 3 级[18]。另在既往一线内分泌治疗失败人群中,中位 PFS 为 9.6 个月,对比 BOLERO-2 试验(绝经后 HR 阳性晚期乳腺癌既往 AI 治疗失败后接受依维莫司联合依西美坦治疗)PFS 为 10.6 个月[19],PALOMA-3 试验(HR 阳性晚期乳腺癌接受哌柏西利联合 FUL 治疗)PFS 为 9.5 个月[20]。节拍化疗同期内分泌治疗可获得与以上旨在逆转内分泌耐药的临床试验相似的 PFS 获益且副反应较小,但由于样本量仅有 44 例,该结果证据力度不足以证实同期治疗临床获益更佳。

招募了 41 例既往接受≤一线内分泌治疗的绝经后 HR 阳性晚期乳腺癌患者的二期单臂前瞻性临床试验,给予节拍口服卡培他滨同期 FUL 治疗,中位治疗期 11 个月时,总人群中位 PFS 为 14.98 个月,疾病进展时间(time to progression, TTP)为 26.94 个月,明显改善了患者生存结果且耐受性良好[21]。

多项二期临床试验及病例报告表明卡培他滨节拍化疗联合新型内分泌药物可使 HR 阳性晚期乳腺癌患者症状迅速缓解,显著提高疗效[22-25]。基于现有的证据,我们可以合理地假设,卡培他滨节拍化疗同期 AI 或 FUL 有望成为 HR 阳性晚期乳腺癌的又一治疗选择,但未来仍需更多大型的Ⅲ期随机对照临床试验去探求。

2.2　*HR 阳性局部晚期乳腺癌新辅助治疗*　新辅助治疗可显著提高局部晚期乳腺癌患者手术率及保乳率。HR 阳性患者占比最高,但对化疗的敏感性差,病理完全缓解(pathological complete response, pCR)率相较于三阴型或 HER2 阳性型的 50%~60%,仅有 10%~20%[26],因此迫切需要可提高该亚型患者新辅助治疗缓解率的治疗策略。

2012 年至 2020 年间多项对比 HR 阳性乳腺癌患者新辅助化疗联合内分泌治疗与单化疗或单内分泌治疗疗效的小样本临床试验、回顾性研究得到了相互矛盾的结论[27-29],这些试验局限于纳入病例数过少,或对 HR 状态及绝经状态未加以限制,仍需进一步探究该治疗模式的临床应用价值。

CBCSG 036 试验作为一项对比化疗同期联合或不联合内分泌治疗的新辅助治疗疗效的前瞻性临床试验,共入组了 249 例ⅡB~ⅢC 期 HR 阳性 HER2 阴性女性乳腺癌患者,绝经前患者的内分泌治疗方案为来曲唑联合促性腺激素释放激素类似物(gonadotropin-releasing hormone analogue, GnRHa),绝经后患者为来曲唑。该研究主要终点是客观缓解率(objective response rate, ORR),中位随访 26 个月时,同期组相较于单化疗组,ORR 显著提高(84.8% *vs* 72.6%,$P=0.02$),且两组的不良事件发生率无显著差异,尤其是 Ki-67>20%亚组(91.2% *vs* 68.7%,$P=0.001$)。在基线 Ki-67 >20%亚组中,同期组和单化疗组 2 年 PFS 率分别为 91.5%、76.5%($P=0.058$),同期组具有 PFS 获益趋势[30]。对于高 Ki-67 的 HR 阳性局部晚期乳腺癌患者而言,新辅助化疗同期内分泌治疗不失为一个有前景的临床策略。纵观近年来多项比较新辅助化疗同期内分泌治疗与单化疗或单内分泌治疗疗效的小型临床试验发现,同期方案表现出良好的临床获益且安全性可控[31-33]。这对于既往的同期治疗影响治疗效果且加重不良反应的观点是一种挑战,也促使对 HR 阳性 HER2 阴性乳腺癌新辅助全身治疗的最佳方案及时机的重新思考。更多大型的临床试验提供长期的生存数据以筛选适宜人群是迫切需要的。

2.3　*HR 阳性早期乳腺癌辅助治疗*　美国国立综合癌症网络(NCCN)指南推荐 HR 阳性早期乳腺癌辅助化疗序贯内分泌治疗,其证据来源于 2002 年 ASCO 大会公布的 SWOG 8814 的 6 年 DFS 数据。基于同一证据,2005 年的圣加仑共识也推荐 HR 阳性中高危乳腺癌辅助化疗序贯内分泌治疗[34]。但该试

验未评估 HER-2 的状态，HER-2 阳性患者所占比例也难以估计。除此之外，2009 年公示的 SWOG 8814 的最终数据表明化疗序贯内分泌治疗与同期治疗的 9 年 DFS（$P=0.061$）及 OS（$P=0.030$）并无显著差异[35]。在此期间多项针对 HR 阳性 HER2 阴性乳腺癌辅助化疗联合内分泌治疗的小样本前瞻性临床试验得到的结论也是相互矛盾的。

目前辅助化疗同期内分泌治疗的临床试验研究对象大多为绝经后患者，针对绝经前女性的研究资料较少。Regan 等[36]探索性地分析了 TEXT&SOFT 研究中部分数据，中位随访 5 年时，诊断年龄<40 岁亚组辅助化疗同期内分泌治疗组和序贯组的无病间隔（disease-free interval, DFI，$P=0.72$）和无远处复发间隔（distant recurrence-free interval，DRFI，$P=0.86$）均无显著差异[36]。另外 2019 年 ASCO 大会公布的一项系统回顾和贝叶斯网络荟萃分析显示总体上 HR 阳性女性乳腺癌患者辅助化疗同期内分泌治疗和序贯治疗表现出同等疗效，但亚组分析显示，虽然绝经前患者化疗序贯 TAM 组的 DFS 和 OS 优于两者同期组；但化疗同期卵巢功能抑制（ovarian function suppression, OFS）+TAM/AI 组的 DFS 和 OS 均优于序贯方案[37]。多项大型临床研究表明部分年轻乳腺癌患者化疗后仍能恢复卵巢功能，这显示了年轻女性早期开始内分泌治疗的必要性，且化疗同期 GnRHa 相较于单化疗方案可显著降低绝经前女性卵巢早衰率，保留其生育能力[38-40]。因此绝经前 HR 阳性尤其是具有生育要求的乳腺癌患者推荐化疗同期 OFS+TAM/AI 方案治疗。

2021 年正式发表的 POTENT 研究探究了 HR 阳性 HER2 阴性早期中高危乳腺癌患者在术后（既往患者可接受新辅助化疗、内分泌治疗及辅助化疗）接受 S-1 同期标准内分泌方案强化治疗的有效性及安全性。纳入的 1 959 例患者按 1∶1 随机分为同期组及单内分泌组，主要终点为随访患者的无浸润性疾病生存（invasive disease-free survival, iDFS）。中位随访 52.2 个月时，同期组相较于单内分泌组，iDFS 事件显著降低（11% *vs* 16%，HR 0.63，95%*CI*：0.49～0.81，$P=0.0003$），且不良事件与既往报告的 S-1 安全性数据相一致，是可控、可接受的。另外 S-1 同期内分泌治疗的获益不受大部分临床病理因素影响，因此该治疗方案可能成为许多 HR 阳性乳腺癌患者辅助强化治疗的新选择[41]。

3　展　望

精准医学的快速发展也使得临床实践也越来越注重个体化医疗的发展，但目前临床上对于中高危 HR 阳性乳腺癌患者而言，无论是早期辅助治疗、局部晚期新辅助治疗还是晚期解救治疗，也不论月经情况和使用哪种化疗药物、内分泌药物，指南均推荐化疗序贯内分泌治疗。HR 阳性乳腺癌具有高度异质性，且随着对其恶性生物学行为的深入研究以及新药物的研制，关于化疗同期内分泌治疗影响治疗效果这一结论的争论也越来越多。笔者认为，化疗同期内分泌治疗具有其合适的目标人群，在临床应用上具备可行性，不同内分泌药物及不同化疗药物同期使用的疗效存在差异。对于难以耐受常规剂量化疗的晚期患者而言，口服氟尿嘧啶类药物节拍化疗同期非 TAM 类内分泌药物是可供选择的一种方式；对于 Ki-67 高表达或是保乳意愿强烈的局部晚期乳腺癌患者，新辅助化疗同期 AI 治疗方案值得进一步探究其可行性；而对于具有生育要求的早期乳腺癌女性而言，化疗同期 OFS 及 TAM/AI 治疗方案在保护卵巢的同时可显著提高患者预后，除此之外辅助 S-1 同期内分泌强化治疗对于早期中高危患者而言也不失为一个有前景的治疗策略。这说明 HR 阳性乳腺癌患者的治疗并不是一成不变的。越来越多的治疗策略的挖掘及新型内分泌和化疗药物的发展不断扩充临床选择，需要进一步在临床、基础和转化研究来探索合理的联合策略、最佳的治疗时机和目标人群。此外在临床实践中，要注意区别亚型及疾病治疗阶段、既往治疗方案以及患者个体差异性，要个体化对待、精准化治疗。

利益冲突　无

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