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# 甲磺酸阿帕替尼治疗乳腺癌的研究进展：从机制到临床实践

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## 摘　要

**本文系统综述了抗血管生成药物阿帕替尼在乳腺癌治疗中的研究进展与应用前景。乳腺癌是全球高发恶性肿瘤，现有治疗手段如内分泌治疗、化疗、靶向治疗及免疫治疗仍存在局限性，包括特定亚型疗效不足、毒副作用显著、耐药性以及疗效异质性等问题。阿帕替尼作为高选择性VEGFR-2抑制剂，通过阻断PI3K/AKT、NF-κB等下游信号通路，抑制肿瘤血管生成，并可调节免疫微环境，增强抗肿瘤免疫应答。临床前研究表明，阿帕替尼能有效抑制乳腺癌细胞增殖、迁移、侵袭及干细胞活性。临床研究显示，阿帕替尼单药或联合化疗、免疫治疗及放疗在晚期乳腺癌(包括三阴性乳腺癌和HER2阳性型)中表现出一定的疾病控制作用，有助于延长患者无进展生存期与总生存期。其常见不良反应如高血压、手足综合征、蛋白尿等可通过剂量调整与对症支持进行管理。未来研究需进一步探索阿帕替尼与不同疗法的协同作用、个体化给药策略、疗效预测生物标志物，并通过多学科诊疗模式应对耐药与毒性管理问题，以提升其在乳腺癌治疗中的精准性与临床效益。**

## 关键词

**乳腺肿瘤，新生血管化，病理性，阿帕替尼，血管生成抑制剂，血管内皮生长因子受体-2，抗血管生成治疗**

# Research Progress on Apatinib in the Treatment of Breast Cancer: From Mechanism to Clinical Practice

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## Abstract

**This article provides a systematic review of the research progress and application prospects of the anti-angiogenic drug apatinib in the treatment of breast cancer. Breast cancer is a prevalent malignant tumor worldwide, and current treatment modalities—including endocrine therapy, chemotherapy, targeted therapy, and immunotherapy—still face limitations such as insufficient efficacy in specific subtypes, significant toxic side effects, drug resistance, and heterogeneous treatment responses. As a highly selective VEGFR-2 inhibitor, apatinib suppresses tumor angiogenesis by blocking downstream signaling pathways such as PI3K/AKT and NF-κB, while also modulating the immune microenvironment and enhancing anti-tumor immune responses. Preclinical studies have demonstrated that apatinib can effectively inhibit the proliferation, migration, invasion, and stem cell activity of breast cancer cells. Clinical research indicates that apatinib, either as monotherapy or in combination with chemotherapy, immunotherapy, and radiotherapy, exhibits certain disease-controlling effects in advanced breast cancer (including triple-negative breast cancer and HER2-positive subtypes), contributing to prolonged progression-free survival and overall survival in patients. Common adverse reactions such as hypertension, hand-foot syndrome, and proteinuria can be managed through dose adjustment and supportive care. Future studies should further explore the synergistic effects of apatinib with different therapies, individualized dosing strategies, biomarkers for predicting therapeutic efficacy, and address issues of drug resistance and toxicity management through multidisciplinary approaches, so as to enhance the precision and clinical benefits of apatinib in breast cancer treatment.**

## Keywords

**Breast Neoplasms, Neovascularization, Pathologic, Apatinib, Angiogenesis Inhibitors, Vascular Endothelial Growth Factor Receptor-2, Antiangiogenic Therapy**



## 1. 引言

乳腺癌是全球范围内最常见的癌症之一，其发病率在过去几十年中持续上升。根据 2020 年的统计数据，全球新发乳腺癌病例超过 230 万例，死亡人数达到 68.5 万[1]。这种增长趋势预计将在未来继续，至 2040 年，乳腺癌的新发病例可能会超过 300 万，死亡人数将达到 100 万，这种增长主要归因于人口增长和老龄化[1]。虽然当前乳腺癌的治疗取得了一定的进展，但仍然存在诸多挑战与局限性。首先，内分泌治疗在雌激素受体阳性(ER+)乳腺癌中显示出良好的效果[2]。但对于三阴性乳腺癌(TNBC)患者来说，内分泌治疗的效果有限[3]。化疗在乳腺癌治疗中作为基础治疗手段，对三阴性乳腺癌患者展现出核心作用，但其毒副作用仍是主要挑战，不良事件可能导致严重甚至致命的后果[4]。靶向治疗虽突破性提升 HER2 过表达型乳腺癌疗效，仍需克服心脏毒性及耐药(信号旁路激活、靶点异常等)难题[5]。免疫治疗作为一种新兴的治疗策略，通过激活患者自身免疫系统对抗乳腺癌，在 PD-L1 阳性三阴性乳

腺癌治疗中取得了一些进展。但肿瘤异质性和耐药性导致疗效差异显著，需发展多模式联合疗法及精准化策略以突破瓶颈[4] [6]。近年来已有体内和体外研究发现抗血管生成药物阿帕替尼也对乳腺癌产生抑制作用，其研究如下。

## 2. 阿帕替尼的作用机制

### 2.1. 药理特性与靶点

阿帕替尼是一种新型的抗血管生成药物，其主要通过抑制血管内皮生长因子受体-2 (VEGFR-2)及其下游通路来发挥作用，从而抑制肿瘤血管生成，进而抑制肿瘤的生长和转移[7] [8]。阿帕替尼的药理学特征不仅体现在其核心抗血管生成效应，更展现出独特的广谱激酶抑制优势，包括 c-Kit、RAF1、VEGFR1、VEGFR2 和 VEGFR3，尤其是对 c-Kit 的抑制作用显著[9]。此外，阿帕替尼还通过抑制 PI3K/AKT 信号通路，抑制肿瘤细胞迁移和侵袭[10]。

### 2.2. 抗血管生成机制

肿瘤血管生成是乳腺癌的一个重要病理过程。新生血管中 VEGF 与 VEGFRs 的结合过程被认为为血管生成的核心调控机制[11]。阿帕替尼是一种创新型小分子酪氨酸激酶抑制剂，其抗血管生成机制主要通过阻断 VEGF 信号通路实现[7]。阿帕替尼通过靶向 VEGFR-2，从而有效抑制肿瘤血管生成[12]。此外，阿帕替尼还能够与其他治疗手段协同作用，增强抗肿瘤效果。例如，阿帕替尼能够提高免疫应答率，与单独治疗相比，其缓解效率和生存期更好[13]。综上所述，阿帕替尼不仅通过抑制异常血管形成限制肿瘤进展，还可重塑免疫抑制性微环境，增强免疫检查点抑制剂等治疗的协同效应，显著提升客观缓解率并改善患者生存获益。这种多维度治疗模式提供了科学依据和临床转化方向。

### 2.3. 抗血管生成治疗在乳腺癌中的重要性

抗血管生成治疗在乳腺癌中的重要性不容忽视。乳腺癌是女性中发病率最高的恶性肿瘤之一，其进展高度依赖新生血管生成。血管生成不仅为肿瘤提供氧气营养支持，更促进肿瘤的侵袭。因此，抑制血管生成被认为是乳腺癌治疗中的一个重要策略[14]。在乳腺癌的病理过程中，VEGF 扮演着至关重要的角色，其促进血管新生的功能主要是通过 VEGFR-2 这一受体来实现的[15]。由此可见，VEGF/VEGFR 信号通路在肿瘤血管生成系统中占主导地位，因此该通路成为抗血管生成治疗的重要靶点[16]。

## 3. 阿帕替尼在乳腺癌中的基础研究进展

已有体外研究表明阿帕替尼对三阴性乳腺癌的抗肿瘤和抗血管生成作用，阿帕替尼的抗肿瘤作用也可能通过 VEGFR/PI3K/AKT 信号通路实现[17]。另有研究表明阿帕替尼可通过降低 NF-$\kappa$B 信号通路中 p-p65 和 p65 蛋白的表达，以及增加 MAPK 信号通路中 p38、p-p38、JNK 和 p-JNK 的表达来对 MDA-MB-231 细胞产生影响，从而抑制乳腺癌细胞株 MDA-MB-231 的增殖、迁移和侵袭[18]。值得注意的是，阿帕替尼也可对乳腺癌干细胞产生影响。通过抑制乳腺癌干细胞的 ROR 表达、增殖、肿瘤成球、迁移和侵袭，并诱导其凋亡来产生作用[19]。阿帕替尼也可与化疗药物共同作用对三阴性乳腺癌产生影响。阿帕替尼可以增强顺铂对 MDA-MB-231 细胞的抗增殖，促凋亡以及对迁移和侵袭的抑制作用[20]。

## 4. 阿帕替尼在乳腺癌中的临床研究进展

阿帕替尼在乳腺癌中的临床研究进展值得关注，尤其是在单药治疗研究和三阴性乳腺癌(TNBC)中的疗效方面。

### 4.1. 单药治疗研究

在晚期乳腺癌治疗领域，靶向抗血管生成药物正成为破解传统治疗耐药困境的重要突破口。阿帕替尼作为我国自主研发的高选择性 VEGFR-2 酪氨酸激酶抑制剂，其口服给药特性为经多线治疗失败的晚期患者提供了新的单药治疗选择。一项关于阿帕替尼单药治疗晚期乳腺癌的系统回顾和荟萃分析证实了阿帕替尼单药治疗晚期乳腺癌的可靠疗效[21]。有研究报道一例经多线抗 HER2 治疗失败的重度预处理晚期 HER2 阳性乳腺癌患者，在接受阿帕替尼单药治疗(500 mg/d)后实现部分缓解(PR)，无进展生存期(PFS)达 6 个月[22]。由此可见，阿帕替尼单药在晚期乳腺癌治疗中具有多重优势，提示其在重度预处理人群中的潜在获益，为晚期患者提供便捷、可持续的靶向治疗选择。但该个案报告由于其样本量仅为 1 例，证据等级较低，其结果需谨慎解读，不能直接外推至更广泛的患者群体。

### 4.2. 联合治疗策略

在乳腺癌治疗领域，阿帕替尼作为靶向血管生成的关键药物，其临床应用潜力日益凸显。最新研究趋势显示，该药物联合化疗、免疫治疗及放射治疗等的治疗方案已成为研究焦点。

已知在临床治疗中，抗血管治疗联合化疗可有效改善晚期乳腺癌的临床疗效[23]。且阿帕替尼与化疗药物的联合应用已在多种癌肿中治疗中显示出增强的抗肿瘤效果[24]-[26]。在乳腺癌中，有研究数据表明，阿帕替尼单药治疗方案的中位无进展生存期(PFS)维持在 3.3 至 4.6 个月区间，而通过与化疗药物联用可显著延长至 4.4~6.9 个月[27]。基于一项多中心真实世界回顾性数据分析显示，采用阿帕替尼与化疗联合方案治疗 HER2 阴性转移性乳腺癌(含 TNBC 病例)时，显示出 PFS 为 4.7 个月，OS 为 15.3 个月。该研究还指出，携带 BRCA 突变的患者具有更长的 PFS 和 OS，提示阿帕替尼在此亚组中的疗效可能是一个潜在的生物标志物[28]。一项关于 TNBC 患者的研究结果提示，与单纯化疗相比，阿帕替尼联合治疗方案可显著提升疾病控制率(DCR)，并在无进展生存期(PFS)和总生存期(OS)方面展现出更优的临床获益[29]。其次，阿帕替尼与免疫治疗的结合也引起了广泛关注。PD-1/PD-L1 抑制剂作为免疫检查点抑制剂，能够解除肿瘤对免疫系统的抑制，从而增强机体的抗肿瘤免疫反应。针对多种实体瘤的临床治疗研究证实，将 PD-1/PD-L1 检查点抑制剂与血管生成抑制剂联合使用可产生协同抗肿瘤效应[30]。联合策略在提高治疗效果的同时，也可能带来同步的免疫相关毒性反应，因此需要谨慎管理，实现疗效与安全性的精准平衡。最后，阿帕替尼与放疗的联合应用也被认为具有潜力。放疗通过高能射线破坏肿瘤细胞的 DNA 来杀伤肿瘤，而阿帕替尼通过抑制肿瘤血管形成来限制肿瘤的氧供和营养输送，两者的结合可能在不同机制上协同作用，从而提高治疗效果。另有临床研究表明，对于晚期胰腺癌患者，相较于单一放疗方案，阿帕替尼与放射治疗联用可显著提升临床疗效，且治疗过程中未出现超出预期的安全性问题[31]。该研究为阿帕替尼联合放疗提供了初步证据，但研究对象为胰腺癌，其结论不能直接移植到乳腺癌。乳腺癌中关于此联合方案的临床研究数据极少，其协同效应、最佳序贯时机及放射性损伤风险等关键问题均有待探索。综上所述，阿帕替尼在乳腺癌多模式治疗中展现出多维度的协同增效潜力。通过与化疗、免疫治疗和放疗的结合，阿帕替尼可能为乳腺癌患者提供更为有效的治疗方案。但需强调，不同联合方案的剂量优化时序、毒性叠加风险及生物标志物导向的精准匹配仍需通过前瞻性大样本研究建立循证医学证据，特别是在分子分型与肿瘤微环境异质性背景下，需构建标准化评估体系以验证其临床转化价值。

## 5. 安全性及不良反应管理

在乳腺癌的治疗中，阿帕替尼显示出一定的疗效，但同时也伴随着一些常见的不良反应，如高血压、手足综合征和蛋白尿等[28] [32]。高血压是阿帕替尼治疗过程中最常见的不良反应之一[32]。研究表明，高血压的发生率较高，且通常在治疗开始后的几周内出现，但通过对症治疗能够得到很好的控制[33]。手

足综合征也是阿帕替尼治疗中的常见不良反应，这种反应虽然不危及生命，但可能会影响患者的生活质量[28] [34]。蛋白尿则是阿帕替尼治疗中另一个需要关注的不良反应。对于部分病例，采取暂时停药、减少药物用量、针对症状进行治疗以及实施强化护理措施等方法，通常能够在较短时间内实现症状的有效缓解。总之，阿帕替尼在乳腺癌治疗中的不良反应管理需要多学科团队的协作，通过建立系统化监测评估机制并制定精准化干预策略，可显著提升患者用药依从性及生存质量。

## 6. 未来展望

甲磺酸阿帕替尼作为靶向 VEGFR-2 的国产原研药物，通过抑制肿瘤血管生成、调控肿瘤微环境及多靶点激酶抑制特性，为乳腺癌治疗提供了创新性策略。其核心机制不仅局限于阻断 VEGF/VEGFR 信号通路，还可通过抑制多个下游通路协同抑制肿瘤增殖与转移，展现出多维抗肿瘤效应。虽然临床研究进一步验证了其在乳腺癌中的价值，但其广泛应用仍面临挑战。如阿帕替尼与化疗、放疗、免疫治疗及其他抗肿瘤疗法联合应用的大型研究仍然较为欠缺。总之，甲磺酸阿帕替尼为代表的抗血管生成治疗为乳腺癌提供了重要突破口，但其全面临床应用需跨越现有证据不足、耐药性及毒性管理的多重壁垒。通过多学科协作、技术创新及精准医学策略的整合，有望推动乳腺癌治疗从“单一靶向”向“多维调控”的范式转变，最终实现患者生存率与生活质量的同步提升。

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