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# 三阳性乳腺癌治疗策略研究进展

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## 摘　要

**三阳性乳腺癌(Triple-Positive Breast Cancer, TPBC)是一类同时表达人表皮生长因子受体2 (HER2)、雌激素受体(ER)和孕激素受体(PR)的特殊乳腺癌亚型，约占所有乳腺癌的10%~15%。其生物学行为兼具HER2阳性乳腺癌的侵袭性和激素受体阳性乳腺癌的内分泌依赖性，且存在HER2与ER通路的复杂交叉对话，导致治疗响应异质性显著，临床管理面临独特挑战。本文系统综述了TPBC的生物学特征与分子机制，详细阐述了当前针对HER2靶向治疗、内分泌治疗及联合治疗的临床研究证据，探讨了新型治疗策略的研发进展，并对未来精准治疗方向进行展望，旨在为TPBC的临床实践和研究提供全面参考。**

## 关键词

**三阳性乳腺癌，HER2靶向治疗，内分泌治疗，精准治疗**

# Research Progress in Therapeutic Strategies for Triple-Positive Breast Cancer

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## Abstract

**Triple-positive breast cancer (TPBC) is a special subtype of breast cancer with co-expression of human epidermal growth factor receptor 2 (HER2), estrogen receptor (ER) and progesterone receptor (PR), accounting for approximately 10%~15% of all breast cancer cases. Its biological behavior combines the invasiveness of HER2-positive breast cancer and the endocrine dependence**

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**of hormone receptor-positive breast cancer, accompanied by complex crosstalk between the HER2 and ER signaling pathways. This results in significant heterogeneity in treatment response and poses unique challenges for clinical management. This paper systematically reviews the biological characteristics and molecular mechanisms of TPBC, elaborates on the current clinical evidence for HER2-targeted therapy, endocrine therapy and combination therapy, explores the research and development progress of novel therapeutic strategies, and looks forward to the future direction of precision treatment. It aims to provide a comprehensive reference for the clinical practice and research of TPBC.**

## Keywords

**Triple-Positive Breast Cancer, HER2-Targeted Therapy, Endocrine Therapy, Precision Treatment**



## 1. 前言

乳腺癌是全球女性发病率最高的恶性肿瘤，根据激素受体(HR，包括 ER 和 PR)和 HER2 的表达状态，可分为不同分子亚型，各亚型在临床特征、治疗响应和预后方面存在显著差异[1]-[3]。三阳性乳腺癌(TPBC)作为其中一类独特亚型，因同时具备 HER2 过表达和 HR 阳性的双重特征，其发病机制、治疗策略和临床结局均区别于其他亚型[4]。过去三十年，HER2 阳性乳腺癌的治疗格局发生了革命性变化，曲妥珠单抗等抗 HER2 药物的应用显著改善了患者预后[5]。然而，TPBC 患者对单纯抗 HER2 治疗的响应率低于 HR 阴性/HER2 阳性乳腺癌，且内分泌治疗易因 HER2 通路激活而产生耐药[6]。随着对 HER2 与 ER 信号通路交叉对话机制的深入理解，以及新型靶向药物的不断涌现，TPBC 的治疗模式逐渐从单一靶向治疗向多通路联合阻断演进[7]。本文基于近年来发表的临床研究、基础实验及系统综述，从生物学特征、治疗策略、新型治疗方向及预后影响因素等方面进行全面梳理，以期为 TPBC 的精准治疗提供理论依据和实践指导。

## 2. 三阳性乳腺癌的生物学特征与分子机制

### 2.1. 亚型定义与临床病理特征

TPBC 的定义为：免疫组织化学(IHC)检测显示 ER 阳性(肿瘤细胞阳性率 ≥ 1%)、PR 阳性(肿瘤细胞阳性率 ≥ 1%)，且 HER2 阳性(IHC 3+或 IHC 2+伴荧光原位杂交扩增) [8]。与其他亚型相比，TPBC 患者发病年龄相对年轻，肿瘤分级多为中－高级别，Ki-67 增殖指数中等偏高，淋巴结转移率较高[9]。其侵袭性介于 HER2 阳性/HR 阴性乳腺癌和 HR 阳性/HER2 阴性乳腺癌之间，一项基于 SEER 数据库的回顾性研究纳入 8277 例 TPBC 患者，发现其 5 年总生存率(OS)为 91.1%~96.3%，10 年疾病特异性生存率(DSS)为 76.2%~94.0%，预后显著受新辅助化疗(NAC)响应状态影响[10]。此外，TPBC 患者中 PR 阴性亚群的预后更差，其 OS 和 DSS 的风险比(HR)分别为 1.63 和 1.79，提示 PR 状态可能是重要的预后分层指标[10]。

### 2.2. 分子机制与信号通路交叉对话

TPBC 的核心生物学特征是 HER2 与 ER 信号通路的双向交叉对话，这也是其治疗耐药的关键机制

[11]。ER 主要通过基因组和非基因组两种方式发挥作用：基因组途径中，ER 与雌激素结合后形成二聚体，结合到靶基因的雌激素反应元件(ERE)上调控基因转录；非基因组途径中，ERα 可磷酸化丝裂原活化蛋白激酶(MAPK)和生长因子受体(GFR)家族成员[12]。HER2 则通过形成同源或异源二聚体(优先与 HER3 结合)，激活下游 MAPK/PI3K/AKT 信号通路，促进肿瘤细胞增殖、侵袭、抗凋亡和血管生成[13]。在 TPBC 细胞中，HER2 可通过酪氨酸激酶结构域磷酸化激活 ER，而 ER 也可反过来调控 HER2 及其下游通路的活性，形成恶性循环[14]，导致单纯抗 HER2 或内分泌治疗效果不佳，如他莫昔芬在 HER2 过表达情况下可能表现为激动剂活性[15]。

基于 PAM50 分型，TPBC 主要包含管腔型(Luminal A/B，占 71%)和 HER2 富集型(占 29%) [16]，管腔型对内分泌治疗相对敏感但抗 HER2 治疗响应较差，HER2 富集型则对双抗 HER2 治疗响应更显著、pCR 率更高[17]。同时，TPBC 中 PI3KCA 突变率约 30%~40%，可导致 PI3K/AKT/mTOR 通路持续激活，进一步增强肿瘤的侵袭性和治疗耐药性[18]。

### 2.3. 耐药机制

#### 2.3.1. 内分泌治疗耐药

TPBC 患者对内分泌治疗的耐药机制复杂，主要包括 ER 通路异常激活、HER2 通路交叉激活及下游信号通路异常等。HER2 过表达可通过磷酸化 ERα 增强其转录活性，导致肿瘤细胞对他莫昔芬等选择性雌激素受体调节剂(SERM)产生耐药[15]；ER 共激活因子(如 AIB1)过表达或共抑制因子(如 PAX2)低表达，可改变 ER 与 HER2 的相互作用，进一步加剧耐药[19] [20]。ESR1 基因突变也是重要耐药原因，TPBC 复发样本中 ESR1 突变率约为 7%，常见 Y537S、D538G 等位点，可导致 ERα 配体非依赖性激活，且增强 ER 与 HER2 的交叉对话，降低内分泌治疗敏感性[21] [22]。

#### 2.3.2. 抗 HER2 治疗耐药

TPBC 对 HER2 靶向治疗的耐药机制主要包括 HER2 通路异常、下游信号通路激活及肿瘤微环境改变等。HER2 异质性表达、HER3/EGFR 等其他 HER 家族成员异常激活，可绕过 HER2 阻断持续激活下游通路[13] [23]。PI3KCA 基因突变是重要分子机制，一项荟萃分析显示，PI3KCA 突变的 TPBC 患者新辅助治疗 pCR 率(7.6%)显著低于野生型(24.4%) [18]，且晚期患者中该突变与更差的预后相关[24] [25]。

## 3. 三阳性乳腺癌的治疗策略

### 3.1. 晚期三阳性乳腺癌的系统治疗

晚期 TPBC 的治疗以抗 HER2 治疗联合内分泌治疗为主，化疗仅用于靶向治疗耐药或肿瘤快速进展患者，方案选择需结合治疗线数、肿瘤负荷、激素受体表达水平及分子特征综合判断。

#### 3.1.1. 一线治疗

CLEOPATR 试验确立了曲妥珠单抗 + 帕妥珠单抗 + 多西他赛作为 HER2 阳性晚期乳腺癌一线标准方案，但其在 TPBC 亚群中的获益略低于 HR 阴性亚群[26]，该试验 5 年随访显示，HR 阳性亚群 OS HR 为 0.74，HR 阴性亚群为 0.64 [27]。后续真实世界研究发现，在双抗 HER2 基础上联合维持内分泌治疗，可进一步改善 TPBC 患者生存且安全性更优[28]。PERTAIN 试验专门针对 TPBC 患者，结果显示双抗 HER2 联合芳香化酶抑制剂(AI)组的中位无进展生存期(mPFS)显著延长(18.9 个月 vs 15.8 个月，HR = 0.65，p = 0.007)，尤其未接受诱导化疗的绝经后患者 OS 获益更显著[29] [30]，支持无化疗指征患者优先采用该方案。新型 ADC 药物德曲妥珠单抗(T-DXd)为一线治疗提供新选择，DESTINY-Breast09 试验初步结果显示，T-DXd ± 帕妥珠单抗疗效优于传统化疗 + 双抗方案，且在 TPBC 亚群中保持一致获益[31]。

#### 3.1.2. 二线及后线治疗

DESTINY-Breast03 试验显示，T-DXd 二线治疗 mPFS (28.8 个月)显著优于恩美曲妥珠单抗(T-DM1，6.8 个月，HR = 0.33，p < 0.0001)，HR 阳性亚群中 T-DXd 的 mPFS 达 26.2 个月，显著优于 T-DM1 [17] [32]。基于此，ESMO 指南推荐 T-DXd 作为 HER2 阳性晚期乳腺癌(包括 TPBC)二线标准治疗，尤其适用于脑转移患者[33]。酪氨酸激酶抑制剂(TKI)在 TPBC 后线治疗中显示一定活性，PHOEBE 试验显示，吡咯替尼+卡培他滨 mPFS (12.5 个月)显著长于拉帕替尼 + 卡培他滨(6.8 个月，HR = 0.39，p < 0.0001)，HR 阳性亚群获益与整体一致[34]；NALA 试验则提示，来那替尼 + 卡培他滨三线及以上治疗中，HR 阳性亚群 PFS 获益不及 HR 阴性亚群[35]。

#### 3.1.3. 内分泌治疗联合 CDK4/6 抑制剂

CDK4/6 抑制剂与抗 HER2、内分泌治疗具有协同作用，Monarc HER 试验显示，阿贝西利 + 曲妥珠单抗 + 氟维司群组 mPFS (8.3 个月)显著优于化疗 + 曲妥珠单抗组(5.7 个月，HR = 0.67，p = 0.051)，客观缓解率(ORR)达 26% [36]，支持抗 HER2 耐药的 TPBC 患者采用该无化疗方案。MUKDEN 01 试验纳入 79 例 II~III 期 TPBC 患者，采用吡咯替尼 + 来曲唑 + 达尔西利新辅助治疗，pCR 率达 30.4%，RCB-0/I 率为 55.7%，Ki67 表达显著下降，安全性良好[37]，为无化疗方案提供新证据。晚期 TPBC 已形成“无化疗为优选、化疗为补充”的格局，T-DXd 解决 HER2 异质性问题，三联方案解决抗 HER2 耐药难题，方案选择需结合分子特征和治疗线数个体化制定。

### 3.2. 早期三阳性乳腺癌的新辅助治疗

新辅助治疗的主要目标是实现 pCR，这是早期乳腺癌患者长期生存的重要预后指标[38]。TPBC 的新辅助治疗需平衡抗 HER2 治疗、内分泌治疗和化疗的作用，以最大化治疗响应并减少不良反应。

#### 3.2.1. 抗 HER2 治疗联合化疗

NeoSphere 试验显示，多西他赛 + 曲妥珠单抗 + 帕妥珠单抗方案在 HER2 阳性乳腺癌中的 pCR 率为 45.8%，但 HR 阳性亚群(22%)显著低于 HR 阴性亚群(55%) [39]；PEONY 试验在亚洲人群中验证了该方案，HR 阳性亚群 pCR 率为 33%，仍低于 HR 阴性亚群的 46% [40]，提示单纯 HER2 联合化疗在 TPBC 中的 pCR 率有限，需探索更优联合策略。

#### 3.2.2. 无化疗新辅助方案

无化疗新辅助方案逐渐成为研究热点，TBCRC 023 试验采用拉帕替尼 + 曲妥珠单抗联合内分泌治疗，治疗 24 周后 TPBC 患者乳腺 pCR (bpCR)率达 33%，不良反应轻微[41]；ADAPT 试验显示，T-DM1±内分泌治疗组 pCR 率(41%)显著高于曲妥珠单抗 + 内分泌治疗组[42]；NA-PHER2 试验采用曲妥珠单抗 + 帕妥珠单抗 + 帕博西利 + 氟维司群四药无化疗方案，pCR 率为 27%，Ki67 表达显著下降，安全性更优[43]，为不耐受化疗患者提供替代选择。早期 TPBC 新辅助治疗呈现“化疗联合为基础、无化疗方案为重要补充”的趋势，未来有望通过分子分型筛选获益人群，扩大无化疗方案应用范围。

### 3.3. 早期三阳性乳腺癌的辅助治疗

辅助治疗的核心目标是降低复发风险，改善长期生存，需基于新辅助治疗响应状态、肿瘤分期和分子特征个体化选择。

#### 3.3.1. 抗 HER2 治疗

NSABP B-31 和 NCCTG N9831 试验确立了曲妥珠单抗联合化疗作为 HER2 阳性早期乳腺癌辅助标准方案，TPBC 患者无病生存期(DFS) HR 为 0.44，显著优于单纯化疗[44]；APHINITY 试验显示，曲妥珠

单抗 + 化疗联合帕妥珠单抗，可进一步改善淋巴结阳性 TPBC 患者 8 年浸润性无病生存期(iDFS)，从85.8%提升至 88.4% (HR = 0.77) [45]。ExteNET 试验显示，来那替尼可显著改善 HR 阳性亚群 5 年 iDFS (HR = 0.60)，FDA 和 EMA 批准其用于 TPBC 辅助治疗[46]；回顾性研究显示，来那替尼剂量递增策略可显著提高治疗完成率(76% vs 40.5%, p = 0.013)，降低腹泻发生率[47]。

#### 3.3.2. 内分泌治疗

辅助内分泌治疗可降低激素依赖性复发风险，EBCTCG 荟萃分析显示，卵巢功能抑制联合 AI 或他莫昔芬可改善 HR 阳性早期乳腺癌患者 DFS，但 HER2 阳性亚群获益不如 HER2 阴性亚群(HR = 1.08 vs 0.65, p = 0.021) [8]；另一项荟萃分析显示，在 HER2 阳性早期乳腺癌中，AI 与他莫昔芬的 DFS 无显著差异(HR = 0.99, p = 0.96) [48]，提示内分泌治疗类型对 TPBC 获益影响有限。

#### 3.3.3. 残留病灶的后续治疗

KATHERINE 试验显示，新辅助治疗后有残留病灶的 HER2 阳性早期乳腺癌患者，辅助 T-DM1 治疗的 iDFS 显著优于曲妥珠单抗(HR = 0.77)，TPBC 亚群获益与整体一致[49]，确立了 T-DM1 作为此类患者的标准辅助方案。早期 TPBC 辅助治疗已形成“抗 HER2 为核心、内分泌为辅助、残留病灶精准强化”的个体化策略，为患者提供全方位复发防控。

### 3.4. 三阳性乳腺癌联合治疗的安全性管理

TPBC 治疗以多药联合为核心，药物副作用叠加成为临床管理重点，其中腹泻、心脏毒性、骨髓抑制最为常见，需针对性制定预防和管理策略，保证治疗顺利进行。

#### 3.4.1. 腹泻的管理

腹泻主要由 TKI 类药物、CDK4/6 抑制剂、抗 HER2 单抗引发，来那替尼腹泻发生率最高(90%以上)，严重时可影响治疗依从性。使用来那替尼、吡咯替尼的患者，可预防性使用洛哌丁胺，来那替尼采用剂量递增策略可降低重度腹泻发生率；1~2 级腹泻予止泻药物及补液，3~4 级腹泻需暂停用药，纠正电解质紊乱后再考虑减量重启。

#### 3.4.2. 心脏毒性的管理

心脏毒性是抗 HER2 治疗的特征性不良反应，主要表现为 LVEF 下降、心力衰竭等，与化疗联用时风险增加。治疗前评估心脏功能，避免抗 HER2 药物与蒽环类等心脏毒性化疗药物长期联用；治疗期间每 3 个月监测 LVEF，出现症状立即检查，LVEF 较基线下降≥10%且<50%需暂停治疗并予心肌营养药物，持续下降或出现心力衰竭需永久停药。

#### 3.4.3. 骨髓抑制的管理

骨髓抑制主要由化疗、CDK4/6 抑制剂引发，中性粒细胞减少最常见。化疗 + 抗 HER2 治疗患者，可预防性使用 G-CSF；CDK4/6 抑制剂治疗期间定期监测血常规，1~2 级中性粒细胞减少予口服升白细胞药物，3~4 级需暂停用药并予 G-CSF，出现发热性中性粒细胞减少需立即抗感染治疗。

#### 3.4.4. 其他不良反应的管理

乏力、恶心呕吐可予止吐药物及营养支持；肝肾功能损伤多为轻中度，定期监测并予保肝护肾药物，重度损伤需暂停用药。

## 4. 三阳性乳腺癌的新型治疗方向

### 4.1. PI3K/AKT/mTOR 通路抑制剂

PI3K/AKT/mTOR 通路是 HER2 与 ER 信号通路交叉对话的关键节点，与 TPBC 治疗耐药密切相关

[50]。BOLERO-3 试验显示，依维莫司 + 曲妥珠单抗 + 长春瑞滨对 HR 阳性亚群无显著获益(HR = 0.93)，仅 HR 阴性亚群 PFS 获益[51]。新型 PI3K 抑制剂为 PI3KCA 突变患者提供新希望，B-PRECISE-01 试验采用 PI3K 抑制剂 MEN1611 + 曲妥珠单抗 ± 氟维司群治疗，缓解率良好[52]；ALPHABET 试验正在比较曲妥珠单抗 + 阿培利司 ± 氟维司群与曲妥珠单抗 + 化疗的疗效，有望为此类患者提供更优选择[53]。

### 4.2. 免疫治疗

免疫检查点抑制剂在 HER2 阳性乳腺癌中的应用仍处于探索阶段。KATE2 试验显示，T-DM1 + 阿替利珠单抗在 PD-L1 阳性亚群中 mPFS 显著延长，但 TPBC 患者获益显著低于 HR 阴性患者(HR = 1.08 vs 0.58) [54]；IMpassion050 试验显示，阿替利珠单抗 + 化疗 + 双抗 HER2 治疗与安慰剂组的 pCR 率无显著差异[55]。TPBC 中 HER2 富集型仅占 29%，肿瘤浸润淋巴细胞(TILs)水平较低，可能是免疫治疗响应率低的原因[56]，未来需探索双抗 HER2 联合免疫检查点抑制剂等更优策略[57]。

### 4.3. 分子分型指导的个体化治疗

TPBC 的分子异质性是治疗响应差异的核心原因，基于 PAM50 分型的个体化治疗成为研究方向。PAMELA 试验显示，HER2 富集型 TPBC 患者新辅助联合治疗 pCR 率(32%)显著高于非 HER2 富集型(5%) [58]；PATRICIA 试验发现，管腔 B 型患者接受帕博西利联合方案 mPFS (10.6 个月)显著长于管腔 A 型(8.2 个月)和 HER2 富集型(4.3 个月) [59]。PI3KCA、TP53 等基因突变可作为治疗选择的生物标志物，其突变与更低的 pCR 率和更差的预后相关[18] [24] [25]，基于分子分型和基因突变的个体化方案可提高治疗疗效。

### 4.4. 新型内分泌治疗药物

新型内分泌治疗药物为 TPBC 患者提供新选择，选择性雌激素受体降解剂(SERD)如氟维司群，可降解 ER 蛋白并与抗 HER2 治疗协同作用[6]；新型口服 SERD 如艾拉司群在 ESR1 突变患者中疗效良好，其与抗 HER2 药物的联合应用正在探索[60]。此外，完全雌激素受体拮抗剂(CERAN)、蛋白酶体靶向嵌合体(PROTAC)等新型药物在临床前研究中显示良好抗瘤活性，有望提供更多治疗选择[60]。

## 5. 预后影响因素与生物标志物

### 5.1. 治疗响应状态

新辅助治疗 pCR 率是 TPBC 患者长期生存的重要预后指标，SEER 数据库研究显示，CR、PR、NR 患者的 5 年 OS 率分别为 96.3%、91.1%和 79.3%，10 年 DSS 率分别为 94.0%、83.4%和 76.2% ($p < 0.001$)，PR 和 NR 是 OS 和 DSS 的独立不良预后因素[10]。

### 5.2. 激素受体状态

PR 状态是 TPBC 的重要预后生物标志物，PR 阴性患者预后更差，与肿瘤侵袭性更强、内分泌治疗响应率更低相关[10] [27]。ER 和 PR 表达水平也影响预后，低水平表达患者更倾向于 HER2 富集型，高水平表达患者更倾向于管腔型[11]。

### 5.3. 分子特征

PI3KCA 和 TP53 基因突变是 TPBC 的不良预后因素，激素治疗耐药患者中其突变率显著高于敏感患者，与肿瘤侵袭性和复发风险密切相关[21]；ESR1 基因突变与内分泌治疗耐药相关，在 TPBC 复发样本

中发生率约为 7% [21]。

### 5.4. 临床病理特征

年龄 ≥ 65 岁、III 期肿瘤、N3 淋巴结转移的 TPBC 患者预后更差[10]；农村居民预后显著差于城市居民(OS HR = 1.43)，可能与医疗资源可及性差异有关[10]。

## 6. 总结与展望

三阳性乳腺癌作为独特的乳腺癌亚型，生物学特征复杂，治疗响应异质性显著。近年来，随着对 HER2 与 ER 信号通路交叉对话机制的深入理解及各类药物的涌现，TPBC 治疗模式已从单一靶向治疗向多通路联合阻断演进，无化疗方案应用逐渐扩大，显著改善了患者生存和生活质量。但 TPBC 治疗仍面临诸多挑战：部分患者对现有联合方案响应不佳，治疗耐药机制尚未完全阐明，分子分型和生物标志物的临床应用仍需验证。未来研究应聚焦于深入探索分子异质性、研发新型靶向药物、优化免疫联合策略、开展更多前瞻性试验，推动基于分子特征的个体化治疗成为核心，进一步提高疗效，改善患者长期生存。

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