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曲妥珠单抗靶向治疗HER2阳性乳腺癌的研究进展

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摘 要

乳腺癌的发展趋势日益增长，其中人表皮生长因子受体2 (HER2)阳性乳腺癌占所有乳腺癌的15%~20%。HER2阳性乳腺癌侵袭性强、复发率高、预后差。随着分子生物学研究的深入，肿瘤靶向治疗的研究和临床应用取得了突破性进展，HER2靶向治疗的进展改善了HER2阳性乳腺癌患者的生存。针对HER2的单克隆抗体、酪氨酸激酶抑制剂和抗体－药物偶联物的引入显著改善了HER2阳性乳腺癌患者的预后。典型的是抗HER2抗体曲妥珠单抗，已被认为是针对HER2阳性肿瘤最有效的治疗药物之一。HER2基因在乳腺癌诊断、治疗及评价预后中具有重要指导价值。本文围绕HER2阳性乳腺癌患者的抗HER2单克隆抗体的靶向治疗做一综述。

关键词

乳腺癌，人表皮生长因子受体-2，曲妥珠单抗，靶向治疗

Research Progress of Trastuzumab Targeted Therapy for HER2-Positive Breast Cancer

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Abstract

Breast cancer is a growing trend, with human epidermal growth factor receptor 2 (HER2) positive

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breast cancer accounting for 15%~20% of all breast cancers. HER2 positive breast cancer is aggressive, has high recurrence rate and poor prognosis. With the deepening of molecular biology research, the research and clinical application of tumor targeted therapy have made breakthroughs, and the progress of HER2-targeted therapy has improved the survival of patients with HER2-positive breast cancer. The introduction of monoclonal antibodies against HER2, tyrosine kinase inhibitors, and antibody-drug conjugates significantly improved outcomes in patients with HER2-positive breast cancer. Typical is the anti-HER2 antibody trastuzumab, which has been recognized as one of the most effective therapies against HER2-positive tumors. HER2 gene has important guiding value in diagnosis, treatment and prognosis evaluation of breast cancer. This review focuses on the targeted therapy of anti-HER2 monoclonal antibodies in patients with HER2 positive breast cancer.

Keywords

Breast Neoplasms, HER2, Trastuzumab, Targeted Therapy

1. 引言

根据 2020 年肿瘤数据库 GLOBOCAN 报告，乳腺癌是女性高发癌症，每年约有 230 万新发病例，平均每年导致 68 万人死亡。发病率和死亡率均居女性癌症的首位[1]。其中 HER2 阳性乳腺癌在乳腺癌各亚型中发病率高。在过去的二十年中，针对 HER2 的单克隆抗体(MoAbs)、酪氨酸激酶抑制剂(TKIs)和抗体–药物偶联物(ADCs)的引入显著改善了疾病阶段的患者预后[2]。2017 年 ESMO 大会上，ExteNET 研究更新了研究结果，中位随访时间 5.2 年，结果显示在曲妥珠单抗治疗的基础上再接受为期 1 年的来那替尼治疗，能够提高 HER2 + 早期乳腺癌患者的 5 年无浸润性肿瘤复发生存率 iDFS (90.2% vs 87.7%, P = 0.0083) [3]。此外，根据 MARIANNE III 期试验结果显示，T-DM1 单药组、T-DM1 联合帕妥珠单抗组、曲妥珠单抗联合紫杉类组的中位无病生存期(PFS)分别为 14.1、15.2、13.7 个月，提示 T-DM1 有良好的抗肿瘤作用及耐受性[4]。其中曲妥珠单抗是一种抗 HER2 胞外区的人源化单克隆抗体，成为目前公认的治疗 HER2 阳性乳腺癌的最主要的 HER2 靶向治疗方法[5] [6]。然而，也存在一些缺点，特别是心脏毒性和耐药性，这在临床使用中引起了人们的注意。因此，了解其作用机制对建立改进的治疗策略至关重要。本文主要对曲妥珠单抗在 HER2 阳性乳腺癌治疗中的研究进展及应用现状作如下综述。

2. 曲妥珠单抗

2.1. 作用机理

曲妥珠单抗(Trastuzumab，商品名赫赛汀)是一种人源化单克隆抗体(免疫球蛋白 G1、IgG1)。IgG1 与 HER2 的结构域 IV 胞外区结合，通过上调 Cdk 抑制剂 p27 和阻断 Akt 和 MAPK 通路[7]引起 G1 期细胞阻滞，导致 HER2 受体的丢失从而抑制细胞的存活和生长机制。HER2 与曲妥珠单抗的相互作用通过多种方式阻止酪氨酸激酶信号传导。它可以阻断 HER2 与其他 HER 受体形成二聚体，并阻断胞外区域的裂解。它还可以诱导被动内吞，从而使靶向受体被溶酶体降解[8]。或者，Trastuzumab 的 Fc 区与效应免疫细胞(如自然杀伤细胞)的 Fcγ 受体III结合，通过抗体依赖的细胞介导的细胞毒作用(antibody-dependent

cell-mediated cytotoxicity, ADCC) [9]杀伤肿瘤细胞。由于靶点的高度特异性，与传统化疗药物相比，细胞毒性副作用减少，因此维持了较高的生活质量[10]。曲妥珠单抗还可以阻止 HER2 异源二聚体的形成，从而下调细胞内 PI3K-Akt 通路。进一步通过原癌基因酪氨酸蛋白激酶 Src/黏着斑激酶(Src/Fak)通路[11]抑制细胞存活机制。有趣的是，曲妥珠单抗已被证明具有抗血管生成特性，降低血管内皮生长因子(VEGF)表达，并可能增加血管通透性[12]。通过 ELISA 法检测治疗组和对照组肿瘤组织中 VEGF-A 浓度(pg/mL)。在第 4 天，ELISA 检测显示，与对照组相比，治疗组肿瘤中的 VEGF 显著降低(P = 0.03) [13]。这被提出来促进药物递送到肿瘤，但它同时与血管副作用有关。

2.2. 临床应用

针对 HER2 基因过表达的乳腺癌的单克隆抗体，曲妥珠单抗是全球首个获批上市治疗乳腺癌的靶向药物。曲妥珠单抗作为一种重组人单克隆抗体，其结合于 HER2 胞外结构域 IV，抑制同二聚体的形成，从而阻断下游信号的产生[14]。此外，曲妥珠单抗能与人体免疫细胞作用，产生抗体依赖的细胞毒作用。曲妥珠单抗目前已广泛应用于 HER2 阳性乳腺癌患者的新辅助治疗、术后辅助 s 治疗及晚期解救治疗，均取得了良好的抗肿瘤效果。曲妥珠单抗的临床应用不仅改变了早期 HER2 阳性乳腺癌患者的预后，也成为 HER2 阳性复发转移性乳腺癌一线及疾病进展后的标准治疗方案[15]。在目前乳腺癌临床治疗中占据主导地位。

2.3. 局限性

但是，曲妥珠单抗有几个局限性。首先，它并不是对每一个 HER2 阳性的患者都有效，甚至在那些敏感的患者中，在治疗过程中，相当一部分患者往往会出现耐药。其次，它具有心脏毒性，增加了早期心力衰竭等心脏问题的风险。第三，曲妥珠单抗只靶向受体二聚体中的一个成员，从而防止信号阻断是完全的[16]。由于这些原因，重要的是要研究能够靶向 HER2 受体其他区域的药物，这些药物可以与曲妥珠单抗一起使用。

3. HER2 阳性乳腺癌的研究进展

HER2 阳性乳腺癌约占所有乳腺癌的 15%~20% [17] [18]。这种侵袭性疾病亚型的特征是人表皮生长因子受体 2 (HER2，又称 erbB2)的过度表达，典型的是通过 ERBB2 扩增。HER2 属于受体酪氨酸激酶家族，有 4 个成员：HER1 (又称 EGFR)、HER2、HER3 和 HER4。当 HER 蛋白被激活时，HER 蛋白同源或异源二聚化，随后激活错综复杂的细胞信号级联反应，包括 PI3K-AKT 和 RAS-MAPK (ERK)通路，调节细胞增殖和存活，以及肿瘤细胞的转移[19] [20]。因此，HER2 是乳腺肿瘤的主要致癌驱动因子，过度表达该蛋白，从而提供了一种治疗脆弱性，可以有效地靶向 HER2 阳性肿瘤患者。

HER2 靶向治疗的进展改善了 HER2 阳性乳腺癌患者的生存。局部疾病的标准治疗是化疗和 1 年的辅助 HER2 靶向治疗，典型的是抗 HER2 抗体曲妥珠单抗。尽管这种治疗方法有效，但仍有一部分患者会出现疾病复发[21]。因此，通过联合不同的 HER2 靶向药物或延长 HER2 靶向治疗的持续时间来提高治疗效果已成为人们关注的焦点。事实上，HER2 双靶向治疗、延长疗程的抗 HER2 治疗，以及抗 HER2 抗体-药物偶联物 T-DM1 的辅助治疗，均已被批准用于临床。

目前已开发了几类抗 HER2 药物，包括：1) 与 HER2 胞外区结合的单克隆抗体，如曲妥珠单抗和帕妥珠单抗，它们通过抑制 HER2 信号传导发挥直接抗肿瘤作用，通过与宿主免疫系统的相互作用诱导抗体依赖的细胞毒性从而发挥间接抗肿瘤作用；2) 小分子酪氨酸激酶抑制剂(TKIs)，包括拉帕替尼、奈拉替尼和阿法替尼，可与 HER2 及其他 HER 家族成员的胞内酪氨酸激酶结构域结合；3) 抗体－药物偶联

物(ADCs)，如曲妥珠单抗 emtansine (T-DM1)，由靶向 HER2 胞外区的单克隆抗体与细胞毒剂连接而成[22] [23] [24]。随着 HER2 阳性靶向药物的相继问世，HER2 阳性乳腺癌患者的生存率和预后得到了极大的改善。但是，靶向药物具有一定耐药性。一般来说，对 HER2 靶向药物的耐药可归因于不同的机制，尽管有些可能是不同药物之间共有的，这些机制要么在初始治疗时流行(固有耐药)，要么在治疗过程中出现，因为选择和最终主导了罕见的先前存在或新获得的耐药亚克隆(获得性耐药)。HER 家族受体的不完全抑制，通过未被抑制的 HER 蛋白的代偿信号实现持续的信号传递，是抗 HER2 治疗失败的主要原因[25]。通过联合使用 HER 靶向药物，包括两种抗 HER2 抗体(曲妥珠单抗和帕妥珠单抗)联合使用或与强效 TKI 联合使用，有望克服这一不足，实现对 HER 家族受体的全面抑制[26] [27] [28]。

4. 曲妥珠单抗在 HER2 阳性乳腺癌的治疗进展

4.1. 术前新辅助治疗

GeparQuattro 研究[29]证实蒽环类 + 紫杉类新辅助化疗联合曲妥珠单抗可达到较高的病理完全缓解率(PCR)，且不增加早期不良反应。NOAH 研究[30]结果也显示，与单独化疗组比较，曲妥珠单抗联合化疗组可明显提高 HER2 阳性患者的 pCR 率，并使患者死亡率和复发率分别下降了 33%和 40%。这一结果在炎性乳腺癌的亚组分析中也得到了验证。因此，曲妥珠单抗联合紫杉类化疗为基础的方案，成为 HER2 阳性乳腺癌新辅助治疗的基本方案。在曲妥珠单抗时代，15%~25%的早期 HER2 + 肿瘤患者在接受曲妥珠单抗和化疗，但仍有疾病复发，这可能部分归因于 HER 家族受体的不完全抑制[31] [32]。HER2 双靶向治疗的卓越疗效首次在转移性乳腺癌患者的克莱奥帕特拉试验中得到证实，在曲妥珠单抗和多西他赛的基础上加用帕妥珠单抗，获得了前所未有的 15.7 个月总生存(OS)获益(中位 OS 分别为 56.5 个月和 40.8 个月；HR 0.6)。随后，为了提高 pCR 率，在新辅助治疗中进行了双重 HER2 阻断试验，在曲妥珠单抗和化疗的基础上加用帕妥珠单抗或拉帕替尼，多个试验的结果确实显示了更高的 pCR 率(95% CI 0.56~0.84; P < 0.001) [33]。KRISTINE III 期临床试验显示，HER2 阳性乳腺癌患者的早期新辅助治疗中，曲妥珠单抗 + 帕妥珠单抗 + 化疗方案的 pCR 率比 T-DM1 + 帕妥珠单抗更高，但 T-DM1 + 帕妥珠单抗方案的安全性更佳[34]，可能是与偶联于曲妥珠单抗上抑制微管形成的药物靶向于肿瘤细胞，缺乏整体抗肿瘤的效果有关，并有待于进一步研究。

4.2. 术后辅助治疗

NSABP B-31 与 NCCTG N9831 研究联合分析显示[32] [35]，辅助化疗后添加曲妥珠单抗可将患者的复发风险降低一半，无病生存期(DFS)和总生存期(OS)均得到改善。曲妥珠单抗联合化疗较曲妥珠单抗序贯化疗更能提高 HER2 阳性早期乳腺癌患者的治疗效果。接受曲妥珠单抗辅助治疗的女性 5 年无病生存率为 94.8%，而未接受曲妥珠单抗(P = 0.22)的女性 DFS 为 82.7%。接受曲妥珠单抗辅助治疗的女性 5 年总生存率为 100%，而未接受曲妥珠单抗(P = 0.038)辅助治疗的女性 5 年总生存率为 90.4% [36]。有临床试验证实[37]，术后辅助治疗中的双靶向治疗组的无病生存期与单靶向治疗组比较无明显获益，且双靶向治疗组的腹泻、皮疹等发生率反而高于单靶向治疗组，提示拉帕替尼联合曲妥珠单抗辅助治疗 HER2 阳性乳腺癌并不能改善生存。

4.3. 晚期治疗

Slamon 等[38]领衔的 H0648g 研究首次证实了一线曲妥珠单抗联合化疗(包括蒽环类或紫杉类药物)与单独化疗相比，能提高 HER2 阳性晚期乳腺癌的客观缓解率(objective response, ORR) (50% vs 32%, P < 0.001)，明显延长疾病进展时间(7.4 个月 vs 4.6 个月，P < 0.001)及 OS (25.1 个月 vs 20.3 个月，P = 0.046)。

M77001 研究[39]进一步肯定了上述研究的结果，曲妥珠单抗联合多西他赛作为 HER2 阳性晚期乳腺癌患者的一线治疗优于单独使用多西他赛，并且几乎没有其他毒性。基于 CLEOPATRA 试验[40] [41]，目前推荐的 HER2+晚期乳腺癌患者的一线治疗首选方案为曲妥珠单抗联合帕妥珠单抗与紫杉类。上述研究确立了曲妥珠单抗联合紫杉类在一线标准治疗的地位。此外，Robert 等[42]还发现曲妥珠单抗、紫杉醇联合卡铂疗效优于曲妥珠单抗联合紫杉醇，能提高 ORR (52% vs 36%, P = 0.04)和 PFS (10.7 个月 vs 7.1 个月，P = 0.03)。对于 HER2+的转移性乳腺癌患者，sysucc-002 研究表明，曲妥珠单抗加内分泌治疗的疗效不亚于曲妥珠单抗加化疗，且毒性反应更低。

5. 总结

随着我们对 HER2 + 乳腺癌的基因组特征以及分子和突变进化的了解加深，该领域不可否认地朝着精准医疗的方向发展。毫无疑问，曲妥珠单抗是 HER2 乳腺癌治疗的重大突破，既延长了乳腺癌患者的生命，又挽救了乳腺癌患者的生命。然而，关于最优持续时间和阻力的问题仍然需要更精确的回答。关于心脏毒性的副作用也不应该被忽视，前瞻性的有益方案应该考虑进一步减少这种副作用。展望未来，对 ErbB 受体下游异常的研究可以突出更多针对未来治疗剂的靶点。这些应着重于抑制增强的致瘤潜能，这可能会改善和延长寿命。尽管有这些改善，治疗抵抗的出现仍然是一个常见的和具有挑战性的事件，特别是在晚期疾病环境中，并且严重提醒我们需要更有效的治疗方法。破解耐药机制将为开发有效规避疾病复发的方法奠定基础。在 HER2 阳性乳腺癌患者的综合治疗中，应依据患者的具体病情，做出最有利于患者的组合治疗，最大限度的延长患者的总生存时间，做到真正意义上的个体化精准治疗。

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