·论著·

# 曲妥珠单抗治疗晚期乳腺癌的应用效果与血清学指标观察

王文玉[1,*]　贾欢欢[1]　聂健圳[2]
1.河南科技大学第一附属医院肿瘤内科 (河南 洛阳 471000)
2.河南科技大学第一附属医院手术部 (河南 洛阳 471000)

【摘要】**目的** 分析探究曲妥珠单抗治疗晚期乳腺癌患者的应用效果与血清学指标观察。**方法** 选取2019年6月至2021年6月本院收治的晚期乳腺癌患者130例并进行随机分组，对照组给予常规化疗治疗，研究组给予常规化疗联合曲妥珠单抗治疗。对比2组患者临床疗效、血清学指标以及心脏不良反应发生率。**结果** 2组患者基本资料对比，差异无统计学意义(*P*>0.05)，具有可比性。 研究组治疗总有效率高于对照组(*P*<0.05)。研究组患者化疗后血清ET、VEGF、HIF-1α水平显著低于对照组(*P*<0.05)。对照组心脏不良反应发生率为3.08%(2/65)，与研究组的4.62%(3/65)相近，差异无统计学意义($\chi^2$=0.208，*P*=0.648>0.05)。**结论** 常规化疗联合曲妥珠单抗治疗晚期乳腺癌患者效果确切，可以降低血清学指标水平，且用药安全。

【关键词】曲妥珠单抗；晚期乳腺癌；应用效果；血清学指标
【中图分类号】R737.9
【文献标识码】A
**DOI:**10.3969/j.issn.1009-3257.2022.06.017

# Application Effect and Serological Index Observation of Trastuzumab in the Treatment of Advanced Breast Cancer

WANG Wen-yu[1,*], JIA Huan-huan[1], NIE Jian-zhen[2].
1.Department of Oncology, the First Affiliated Hospital of Henan University of Science and Technology, Luoyang 471000, Henan Province, China
2.Department of Surgery, the First Affiliated Hospital of Henan University of Science and Technology, Luoyang 471000, Henan Province, China

**Abstract:** ***Objective*** To analyze and explore the application effect and serological indexes of trastuzumab in the treatment of patients with advanced breast cancer. ***Methods*** A total of 130 patients with advanced breast cancer who were admitted to our hospital from June 2019 to June 2021 were selected and randomly divided into groups. The control group was given conventional chemotherapy, and the study group was given conventional chemotherapy combined with trastuzumab. The clinical efficacy, serological indexes and the incidence of adverse cardiac reactions were compared between the two groups. ***Results*** There was no significant difference in the basic data of the two groups of patients (*P*>0.05), and they were comparable. The total effective rate of treatment in the study group was higher than that in the control group (*P*<0.05). The serum levels of ET, VEGF and HIF-1α in the study group after chemotherapy were significantly lower than those in the control group (*P*<0.05). The incidence of adverse cardiac reactions in the control group was 3.08 % (2/65), which was similar to 4.62 % (3/65) in the study group, and the difference was not statistically significant ($\chi^2$=0.208, *P*=0.648>0.05). ***Conclusion*** Conventional chemotherapy combined with trastuzumab in the treatment of patients with advanced breast cancer is effective, can reduce the level of serological indicators, and is safe to use.

***Keywords: Trastuzumab; Advanced Breast Cancer; Application Effect; Serological Indicators***

乳腺癌属于妇科恶性肿瘤，是全世界第二大常见的肿瘤，严重威胁女性生命健康[1]。其中手术和化疗是常用治疗乳腺癌的方法[2]。分子生物学和免疫疗法的出现使靶向治疗干预成为可能，提供针对患者和疾病个体特征的治疗[3-4]。人表皮生长因子受体-2(HER-2)的过度表达与乳腺癌的病理生理学有关，是其治疗的临床相关生物标志物[5-6]。曲妥珠单抗是一种靶向HER2的重组抗体，是第一个获批用于治疗HER2阳性乳腺癌的生物药物[7]。多项临床研究表明，曲妥珠单抗在减少乳腺癌患者的复发和死亡方面具有重要作用[8-9]。因此，本研究探讨曲妥珠单抗治疗晚期乳腺癌的应用效果与血清学指标观察，现具体报道如下。

## 1 资料与方法

**1.1 研究对象** 选取2019年6月至2021年6月本院收治的晚期乳腺癌患者130例，年龄39~76岁，平均年龄(52.38 ±7.98)岁。

纳入标准：符合《中国抗癌协会乳腺癌诊治指南与规范(2017年版)》[10]中关于乳腺癌的诊断标准，患者经病理检查确诊为乳腺癌；临床资料完整者；患者签署自愿受试同意书，患者及其家属需签署知情同意书。排除标准：合并高血压、糖尿病、高脂血症患者；合并其他恶性肿瘤患者；合并其他器官严重性病变患者。

**1.2 治疗方法** 对照组根据晚期乳腺癌的化疗标准进行常规化疗。研究组接受常规化疗联合曲妥珠单抗(上海复宏汉霖生物制药有限公司，国药准字S20200019)治疗：首次负荷剂量8mg/kg后，以8mg/kg剂量每3周1次给药。

**1.3 疗效评定和不良反应** 行血、尿常规及肝、肾功能检查，进行CT检查，观察病灶进展情况以及不良反应发生情况，疗效判定可分为完全缓解(CR)：靶病灶消失；部分缓解(PR)：基线病灶长径缩小程度>30%；稳定(SD)：基线病灶长径缩小≤30%；疾病进展(PD)：基线病灶长径综合增加程度超过

【第一作者】王文玉，女，住院医师，主要研究方向：乳腺癌。E-mail：Y18438602577@163.com
【通讯作者】王文玉

20%。其中*客观缓解率(ORR)=CR+PR/总例数×100%*。比较两组患者治疗期间的心脏不良反应发生率。

**1.4 血清学指标监测** 检测2组患者治疗前后血清学指标水平，包括血管内皮生长因子(VEGF)、缺氧诱导因子-1α(HIF-1α)内皮素(ET)。

**1.5 统计学分析** 收集的实验数据使用SPSS 21.0进行分析，符合正态分布的计量资料采用 $\bar{x}\pm s$表示，两组比较采用独立样本t检验，计数资料以例数或率表示，两组比较采用 $\chi^2$检验，*P*<0.05为差异具有统计学意义。

## 2 结 果

**2.1 2组基线资料比较** 两组患者基本资料对比，差异无统计学意义(*P*>0.05)，具有可比性，见表1。

**表1 2组基线资料对比**

| 临床病理参数 | | 对照组(n=65) | 研究组(n=65) | t/$\chi^2$ | *P* |
|---|---|---|---|---|---|
| 年龄(岁) | | 53.38±5.35 | 51.76±5.12 | 1.764 | 0.080 |
| 患病时间(年) | | 6.43±0.27 | 6.37±0.24 | 1.339 | 0.183 |
| 肿瘤分期 | Ⅲ | 44 | 39 | 0.833 | 0.361 |
| | Ⅳ | 21 | 26 | | |

**2.2 2组患者治疗效果比较** 研究组治疗总有效率高于对照组，差异有统计学意义(*P*<0.05)，见表2。

**表2 2组患者临床疗效比较[n(%)]**

| 组别 | n | 完全缓解 | 部分缓解 | 稳定 | 进展 | 总有效率 |
|---|---|---|---|---|---|---|
| 对照组 | 65 | 0(0) | 12(18.46) | 29(44.62) | 24(36.92) | 12(18.46) |
| 研究组 | 65 | 5(7.69) | 41(63.08) | 13(20.00) | 6(9.23) | 46(70.76) |

**2.3 2组患者化疗后血清学指标水平比较** 研究组患者化疗后血清ET、VEGF、HIF-1α水平显著低于对照组，差异有统计学意义(*P*<0.05)，见表3。

**表3 2组患者化疗后血清学指标水平比较(pg/mL)**

| 组别 | ET | VEGF | HIF-1α |
|---|---|---|---|
| 研究组(n=65) | 46.87±1.87 | 201.54±5.29 | 126.09±4.37 |
| 对照组(n=65) | 54.75±1.96 | 245.75±6.02 | 156.76±4.98 |
| t | 23.452 | 44.476 | 37.321 |
| *P* | <0.001 | <0.001 | <0.001 |

**2.4 2组患者心脏不良反应发生率** 对照组心脏不良反应发生率为3.08%(2/65)，与研究组的4.62%(3/65)相近，差异无统计学意义($\chi^2$=0.208，*P*=0.648>0.05)。

## 3 讨 论

HER2蛋白的过度表达、HER2基因的扩增或两者都发生在15%到25%的乳腺癌中，并且与肿瘤的侵袭性行为有关[11-12]。曲妥珠单抗在临床上仍然是新辅助、辅助和转移环境中HER2阳性乳腺癌现代护理标准治疗方案的基础组成部分[13]。曲妥珠单抗作用机制的早期研究集中在曲妥珠单抗抑制促肿瘤生长的 HER2 信号通路[14]。随后的研究表明，曲妥珠单抗还可以利用患者的免疫系统来促进抗肿瘤反应[15]。研究发现曲妥珠单抗与自然杀伤细胞(NK)上的Fc受体结合以促进抗体依赖性细胞毒性 (ADCC)的能力[16-17]。有研究进一步阐明了曲妥珠单抗与巨噬细胞上的 Fc-γ受体结合并促进抗体依赖性细胞吞噬作用(ADCP)[18]。曲妥珠单抗可作为抗HER2阳性乳腺癌治疗的首要选择[19]。已有研究显示每周或每三周一次单独给药或与化疗联合给药对HER2阳性转移性乳腺癌患者有益[20-21]。曲妥珠单抗与化疗通常发生的不良事件无关，例如脱发、骨髓抑制和严重的恶心和呕吐[22]。除了在第一次输注时需要注意偶尔出现的超敏反应外，心脏毒性(主要是充血性心力衰竭)是曲妥珠单抗最重要的不良反应[23-24]。本研究中研究组治疗总有效率高于对照组。对照组心脏不良反应发生率为3.08%(2/65)，与研究组的4.62%(3/65)相近，差异无统计学意义($\chi^2$=0.208，*P*=0.648>0.05)。

乳腺肿瘤细胞产生许多可溶性因子，可调节乳腺肿瘤内癌细胞亚群之间的串扰[25]。这些因素中的大多数不仅对肿瘤的增殖和进展至关重要，而且对乳腺癌细胞的转移也很重要[26]。在这些分泌因子中，ET作为乳腺癌细胞生长、进展和转移的重要因素而备受关注[27]。血管生成通过促进肿瘤相关新血管的形成在肿瘤进展中发挥重要作用[28]。血管生成有助于转移扩散，因为它使肿瘤细胞能够进入循环系统，并推动转移前血管生态位的形成[29]。以缺氧为特征的癌症干细胞生态位经历了代谢转变为更具侵入性的程序，并通过产生高水平的促血管生成因子如VEGF来促进肿瘤新血管形成[30-31]。HIF-1α是各种肿瘤细胞代谢的重要调节因子[32]。激活后，HIF-1α 通过直接诱导许多细胞代谢基因的表达来增强有氧糖酵解[33-34]。乳腺癌细胞的发展与缺氧有关[35]。HIF-1α 通过新血管形成影响转移。有研究发现HIF-1α 与乳腺癌转移和较差的患者存活率有关[36]。本研究中研究组患者化疗后血清ET、VEGF、HIF-1α水平显著低于对照组，差异有统计学意义(*P*<0.05)。

综上所述，常规化疗联合曲妥珠单抗治疗晚期乳腺癌效果确切，降低血清学指标水平，用药安全，值得在临床上推广。但是本研究具有一定的局限性，首先，纳入的样本量较少，中心单一，需要进行大规模、多中心的研究来进一步证实。

## 参考文献

[1]马友龙,司景元,延靖蕾,等.HPV16感染乳腺癌MCM7、PD1、PD-L1表达水平及其临床意义[J/OL].中华医院感染学杂志,2021(24):3742-3746.
[2]金小红,顾冬梅,张燕萍,等.乳腺癌化疗导管相关性血流感染外周血TM和TF及CGRP水平变化[J/OL].中华医院感染学杂志,2021(23):3576-3580.
[3]Marcinkowska M,Stanczyk M,Janaszewska A,et al.Multicomponent conjugates of anticancer drugs and monoclonal antibody with PAMAM dendrimers to increase efficacy of HER-2 positive breast cancer therapy[J].Pharm Res,2019,36(11):1-17.
[4]Nasrollahpour H,Isildak I,Rashidi M R,et al.Ultrasensitive bioassaying of HER-2 protein for diagnosis of breast cancer using reduced graphene oxide/chitosan as nanobiocompatible platform[J].Cancer Nanotechnology,2021,12(1):1-16.
[5]Carvajal S,Fera S N,Jones A L,et al.Disposable inkjet-printed electrochemical platform for detection of clinically relevant HER-2 breast cancer biomarker[J].Biosens Bioelectron,2018,104:158-162.

[6]Goldstein L J,Perez R P,Yardley D,et al.A window-of-opportunity trial of the CXCR1/2 inhibitor reparixin in operable HER-2-negative breast cancer[J].Breast Cancer Res,2020,22(1):1-9.
[7]Von Minckwitz G,Huang C S,Mano M S,et al.Trastuzumab emtansine for residual invasive HER2-positive breast cancer[J].N Engl J Med,2019,380(7):617-628.
[8]Modi S,Saura C,Yamashita T,et al.Trastuzumab deruxtecan in previously treated HER2-positive breast cancer[J].N Engl J Med,2020,382(7):610-621.
[9]Tamura K,Tsurutani J,Takahashi S,et al.Trastuzumab deruxtecan (DS-8201a) in patients with advanced HER2-positive breast cancer previously treated with trastuzumab emtansine: A dose-expansion,phase 1 study[J].Lancet Oncol,2019,20(6):816-826.
[10]中国抗癌协会乳腺癌专业委员会.中国抗癌协会乳腺癌诊治指南与规范(2017年版)[J].中国癌症杂志,2017,27(9):695-759.
[11]吕俊宏,吴政光,蔡长青,等.Her2在介导乳腺癌细胞上皮间质转换中的作用研究[J].罕少疾病杂志,2014,105(4):27-30,37.
[12]陈刘镇,王在国,郑惊雷.P63、P120ctn在Her-2阳性乳腺癌中的表达及临床意义[J].罕少疾病杂志,2021,145(2):32-33.
[13]Malecka K,Pankratov D,Ferapontova E E.Femtomolar electroanalysis of a breast cancer biomarker HER-2/neu protein in human serum by the cellulase-linked sandwich assay on magnetic beads[J].Anal Chim Acta,2019,1077:140-149.
[14]Tolaney S M,Wardley A M,Zambelli S,et al.Abemaciclib plus trastuzumab with or without fulvestrant versus trastuzumab plus standard-of-care chemotherapy in women with hormone receptor-positive, HER2-positive advanced breast cancer (monarcHER): A randomised, open-label,phase 2 trial[J].Lancet Oncol,2020,21(6):763-775.
[15]Joensuu H,Fraser J,Wildiers H,et al.Effect of adjuvant trastuzumab for a duration of 9 weeks vs 1 year with concomitant chemotherapy for early human epidermal growth factor receptor 2-positive breast cancer: The SOLD randomized clinical trial[J].JAMA oncol,2018,4(9):1199-1206.
[16]Narayan P,Osgood C L,Singh H,et al.FDA approval summary: Fam-trastuzumab deruxtecan-nxki for the treatment of unresectable or metastatic HER2-positive breast cancer[J].Clin Cancer Res,2021,27(16):4478-4485.
[17]Li G,Guo J,Shen B Q,et al.Mechanisms of acquired resistance to trastuzumab emtansine in breast cancer cells[J].Mol Cancer Ther,2018,17(7):1441-1453.
[18]Dong H,Wang W,Chen R,et al.Exosome-mediated transfer of lncRNA-SNHG14 promotes trastuzumab chemoresistance in breast cancer[J].Int J Oncol,2018,53(3):1013-1026.
[19]Hunter F W,Barker H R,Lipert B,et al.Mechanisms of resistance to trastuzumab emtansine (T-DM1) in HER2-positive breast cancer[J].Br J Cancer,2020,122(5):603-612.
[20]Ma F,Ouyang Q,Li W,et al.Pyrotinib or lapatinib combined with capecitabine in HER2-positive metastatic breast cancer with prior taxanes,anthracyclines,and/or trastuzumab: a randomized, phase II study[J].J Clin Oncol,2019,37(29): 2610-2619.
[21]Emens L A,Esteva F J,Beresford M,et al.Trastuzumab emtansine plus atezolizumab versus trastuzumab emtansine plus placebo in previously treated,HER2-positive advanced breast cancer (KATE2): A phase 2, multicentre,randomised, double-blind trial[J].Lancet Oncol,2020,21(10):1283-1295.
[22]Guglin M,Krischer J,Tamura R,et al.Randomized trial of lisinopril versus carvedilol to prevent trastuzumab cardiotoxicity in patients with breast cancer[J].J A Coll Cardiol,2019,73(22):2859-2868.
[23]Rugo H S,Im S A,Cardoso F,et al.Efficacy of margetuximab vs trastuzumab in patients with pretreated ERBB2-positive advanced breast cancer: A phase 3 randomized clinical trial[J].JAMA Oncol,2021,7(4):573-584.
[24]Loi S,Giobbie-Hurder A,Gombos A,et al.Pembrolizumab plus trastuzumab in trastuzumab-resistant, advanced, HER2-positive breast cancer (PANACEA): A single-arm,multicentre,phase 1b-2 trial[J].Lancet Oncol,2019,20(3):371-382.
[25]Halaka M,Hired Z A,Rutledge G E,et al.Differences in endothelin B receptor isoforms expression and function in breast cancer cells[J].J Cancer,2020,11(9):2688.
[26]Gu X,Han S,Cui M Z,et al.Knockdown of endothelin receptor B inhibits the progression of triple-negative breast cancer[J].Ann N Y Acad Sci,2019,1448(1):5-18.
[27]Maayah Z H,Takahara S,Alam A S,et al.Breast cancer diagnosis is associated with relative left ventricular hypertrophy and elevated endothelin-1 signaling[J].BMC cancer,2020,20(1):1-13.
[28]Kappes L,Amer R L,Sommerlatte S,et al.Ambrisentan, an endothelin receptor type A-selective antagonist, inhibits cancer cell migration, invasion, and metastasis[J].Sci Rep,2020,10(1):1-15.
[29]Tocci P,Blandino G,Bagnato A.YAP and endothelin-1 signaling: an emerging alliance in cancer[J].J Exp Clin Cancer Res,2021,40(1):1-12.
[30]Im E J,Lee C H,Moon P G,et al.Sulfisoxazole inhibits the secretion of small extracellular vesicles by targeting the endothelin receptor A[J].Nat commun,2019,10(1):1-17.
[31]Halaka M,Hired Z A,Rutledge G E,et al.Differences in endothelin B receptor isoforms expression and function in breast cancer cells[J].J Cancer,2020,11(9):2688.
[32]Jin J,Qiu S,Wang P,et al.Cardamonin inhibits breast cancer growth by repressing HIF-1α-dependent metabolic reprogramming[J].J Exp Clin Cancer Res,2019,38(1):1-16.
[33]齐亚莉,吴嘉慧,李忠起,等.miRNA-210通过HIF-1/Notch1信号通路调控乏氧乳腺癌干细胞辐射抗拒的作用[J].国际老年医学杂志,2021,42(6):325-330.
[34]雷建梅,匡文斌,邓秋婵,等.血清HIF-1α、25(OH)D3、IGF-1及SAA水平在不同临床特征乳腺癌患者中的表达及临床意义[J].中国医学创新,2021,18(34):48-52.
[35]Cao L,Wang M,Dong Y,et al.Circular RNA circRNF20 promotes breast cancer tumorigenesis and Warburg effect through miR-487a/HIF-1α/HK2[J].Cell Death Dis,2020,11(2):1-10.
[36]Chen F,Chen J,Yang L,et al.Extracellular vesicle-packaged HIF-1α-stabilizing lncRNA from tumour-associated macrophages regulates aerobic glycolysis of breast cancer cells[J].Nat Cell Biol,2019,21(4):498-510.

(收稿日期：2022-02-03)