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三阴性乳腺癌治疗“中国方案”全球首发 5年无病生存率86.3% 降低复发风险41%

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original reports

Adjuvant Capecitabine With Docetaxel and Cyclophosphamide Plus Epirubicin for Triple-Negative Breast Cancer (CBCSG010): An Open-Label, Randomized, Multicenter, Phase III Trial

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abstract

PURPOSE Standard adjuvant chemotherapy for triple-negative breast cancer (TNBC) includes a taxane and an anthracycline. Concomitant capecitabine may be beneficial, but robust data to support this are lacking. The efficacy and safety of the addition of capecitabine into the TNBC adjuvant treatment regimen was evaluated.

PATIENTS AND METHODS This randomized, open-label, phase III trial was conducted in China. Eligible female patients with early TNBC after definitive surgery were randomly assigned (1:1) to either capecitabine (3 cycles of capecitabine and docetaxel followed by 3 cycles of capecitabine, epirubicin, and cyclophosphamide) or control treatment (3 cycles of docetaxel followed by 3 cycles of fluorouracil, epirubicin, and cyclophosphamide). Randomization was centralized without stratification. The primary end point was disease-free survival (DFS).

RESULTS Between June 2012 and December 2013, 636 patients with TNBC were screened, and 585 were randomly assigned to treatment (control, 288; capecitabine, 297). Median follow-up was 67 months. The 5-year DFS rate was higher for capecitabine than for control treatment (86.3% *v* 80.4%; hazard ratio, 0.66; 95% CI, 0.44 to 0.99; $P = .044$). Five-year overall survival rates were numerically higher but not significantly improved (capecitabine, 93.3%; control, 90.7%). Overall, 39.1% of patients had capecitabine dose reductions, and 8.4% reported grade ≥ 3 hand-foot syndrome. The most common grade ≥ 3 hematologic toxicities were neutropenia (capecitabine, 136 [45.8%]; control, 118 [41.0%]) and febrile neutropenia (capecitabine, 50 [16.8%]; control, 46 [16.0%]). Safety data were similar to the known capecitabine safety profile and generally comparable between arms.

CONCLUSION Capecitabine when added to 3 cycles of docetaxel followed by 3 cycles of a 3-drug anthracycline combination containing capecitabine instead of fluorouracil significantly improved DFS in TNBC without new safety concerns.

ASSOCIATED CONTENT
Appendix
Protocol
Author affiliations and support information (if applicable) appear at the end of this article.
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INTRODUCTION

Triple-negative breast cancer (TNBC) is pathologically defined as an estrogen receptor (ER)–negative, progesterone receptor (PR)–negative, and human epidermal growth factor receptor 2 (HER2)–negative disease.[1] It accounts for 12%-17% of all breast cancers[1] and is characterized by higher relapse rates and shorter overall survival (OS).[2] An understanding of the mechanisms that drive resistance and identification of biomarkers to guide treatment decisions may help to improve survival.[3] To date, anthracycline- and taxane-based therapy remains the sole proven adjuvant systemic approach for prevention of recurrence and survival improvement.[4]

Capecitabine, an oral prodrug of fluorouracil, is metabolized in the liver and malignant tumors and ultimately converted to cytotoxic fluorouracil by thymidine phosphorylase (TP), which is highly expressed in

经过8年努力，一项由复旦大学附属肿瘤医院乳腺外科主任邵志敏教授领衔的三阴性乳腺癌临床试验研究成果，在全球肿瘤学顶尖杂志《Journal of Clinical Oncology》在线发表，影响因子28分。这项被誉为三阴性乳腺癌治疗的“中国方案”证实，在传统化疗基础上联合卡培他滨的辅助化疗方案，使三阴性乳腺癌患者5年无病生存率提高至86.3%，有效降低复发风险41%。

寻找疗效提升最佳化疗“配方”

如今，乳腺癌已经逐渐成为一种可防可治的“慢性病”。但在乳腺癌这个“大家族”中，有一个名为三阴性乳腺癌的亚型，却因雌激素受体、孕激素受体、HER2均表达为阴性，致使内分泌治疗或抗HER2靶向治疗的方案对之疗效甚微，5年内复发转移风险高达20%。

据医院乳腺外科主任邵志敏教授介绍，化疗仍然是三阴性乳腺癌的主要治疗方式。对于早期三阴性乳腺癌患者，术后以蒽环类化疗药物和紫杉醇类化疗药物为基础的辅助化疗是其标准的治疗方案。但患者5年无病生存率仍徘徊在80%左右，已成为生存率的一个“瓶颈”。

是否能在既有的传统化疗方案中，加一些其他药物进而来提高疗效呢？邵志敏教授研究团队始终在寻找这个“配方”。研究团队主要成员、医院乳腺外科副主任医师李俊杰告诉我们，卡培他滨这个化疗药物对复发转移三阴性乳腺癌疗效较为显著，他们曾设想是否可以在传统术后辅助化疗方案中加上这个化疗药物，进而提高三阴性乳腺癌疗效呢？

为了证实这个研究猜想，2012年，由复旦大学附属肿瘤医院牵头、联合中国乳腺癌协作组开起了一项全国多中心、随机、三期、前瞻性的临床试验，旨在寻找这种潜在“配方”可能的有效性。

证实预期疗效提升显著

三阴性乳腺癌接受传统化疗方案患者5年无病生存率始终徘徊在80%左右，难以获得有效突破，也是三阴性乳腺癌治疗中的一个“瓶颈”。

为了证实自己的研究设想，在这项长达8年的临床研究中，邵志敏教授团队在全国35家中心共筛选出636例三阴性乳腺癌患者，最终成功入组并接受治疗的患者有585例，其中试验组297例患者使用了传统化疗方案联合卡培他滨的治疗方案。

研究结果证实，试验组患者较传统方案，显著提高患者无病生存，5年无病生存率从80.4%提高到86.3%，降低34%的事件风险，其中降低复发风险41%，降低远处转移风险37%，总生存率提高了2.6%，极大地改善了三阴性乳腺癌的预后。

“新的化疗方案较传统方案，将三阴性乳腺癌患者的5年无病生存率提高了6个百分点，这验证了我们的预期”，邵志敏教授表示，“我们还欣慰地看到，联合卡培他滨治疗后，患者耐受性良好，血液学不良事件发生率与对照组相当，并没有额外增加患者接受治疗时不可耐受的副反应。”

引领世界有望更大突破

据悉，以往为改善三阴性患者的预后，临床医生大多会选择加大化疗药物的剂量，从而导致患者耐受性相对较差，生存获益甚微。

如今，这项联合卡培他滨辅助化疗的三阴性乳腺癌治疗“中国方案”是中国乳腺癌辅助治疗研究领域首个刊登在《JCO》具有中国自主知识产权的临床研究，它将在保障患者安全性、耐受性的同时，显著提高三阴性乳腺癌患者预后，未来有望写入治疗指南，成为全球三阴性乳腺癌治疗的标准方案。

邵志敏教授还透露，复旦大学附属肿瘤医院乳腺癌研究团队绘制出全球最大的三阴性乳腺癌基因图谱，目前针对晚期三阴性乳腺癌采用多基因组学技术予以分型治疗，治疗策略也将与本研究“携手”，希望在早期乳腺癌中获得更大突破。目前试验团队正在结合、分析、探索对联合卡培他滨方案更为敏感的三阴性亚型，指导后续精准治疗策略的实施。

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