

# 2015 版《中国抗癌协会乳腺癌诊治指南与规范》:药物治疗策略的解读

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**【摘要】** 为推动中国乳腺癌的规范化诊治,中国抗癌协会乳腺癌专业委员会于 2007 年发布了第 1 版《中国抗癌协会乳腺癌诊治指南与规范》(简称《指南》),并结合乳腺癌领域最新循证医学进展每 2 年进行 1 次更新,指导中国乳腺癌的诊断与治疗。最新公布的 2015 版《指南》从乳腺癌筛查、影像诊断、病理诊断、手术及全身治疗等方面对乳腺癌临床诊治策略进行了规范。本文从乳腺癌的内分泌治疗、抗 HER-2 分子靶向治疗、化疗与骨保护治疗的角度出发,对 2015 版《指南》药物治疗策略的更新内容进行了解读。

**【关键词】** 乳腺肿瘤; 药物疗法; 实践指南

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**Clinical Practice Guidelines in Breast Cancer by Chinese Anti-Cancer Association (2015 version): interpretation of updates in terms of systemic treatment** Wang Biyun, Gong Chengcheng, Hu Xichun.  
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**【Abstract】** In order to standardize the management of breast cancer, Chinese Anti-Cancer Association (CACA) issued the first edition of Clinical Practice Guidelines in Breast Cancer in 2007 and updates it every other year based on latest evidences. The newly published CACA Clinical Practice Guidelines in Breast Cancer in 2015 covers the overall management of breast cancer including screening, imaging, pathology, surgery and systemic treatment. This article mainly focused on the updates of systemic treatment for breast cancer patients in 2015 version, with regard to endocrine therapy, anti-HER-2 molecular targeted therapy, chemotherapy and bone protection.

**【Key words】** Breast neoplasms; Drug therapy; Practice guideline

全世界每年新发乳腺癌病例数稳居女性恶性肿瘤之首,中国近年来的乳腺癌发病率亦逐年升高。为推动中国乳腺癌的规范化诊治,中国抗癌协会乳腺癌专业委员会于 2007 年发布了《中国抗癌协会乳腺癌诊治指南与规范》(简称《指南》)<sup>[1]</sup>。最新公布的 2015 版《指南》从乳腺癌筛查、影像诊断、病理诊断、手术及全身治疗等方面分 16 个章节对乳腺癌临床诊治策略进行了规范<sup>[2]</sup>。笔者就其中乳腺癌药物治疗策略进行了解读。

## 一、内分泌治疗方案的选择

激素受体(hormone receptor, HR)阳性的乳腺癌约占全部乳腺癌的 2/3,内分泌治疗是这部分患者辅助治疗及晚期治疗的重要手段。

## 1. 辅助内分泌治疗

针对 HR 阳性乳腺癌的辅助内分泌治疗,他莫昔芬(tamoxifen, TAM)治疗 5 年一直是标准方案。随着 ATLAS<sup>[3]</sup>、aTTom<sup>[4]</sup> 两项大型随机对照研究结果相继公布,延长内分泌治疗时长再次成为关注的焦点。研究提示延长内分泌治疗在 10 年后显示出生存改善,但目前尚无可靠、可临床推广的评估体系筛选可能从延长内分泌治疗中获益的患者<sup>[3,4]</sup>。因此《指南》中仍保留了 2013 版的意见,对于服用 TAM 5 年后仍处于绝经前状态的患者,部分患者(如高危复发)可考虑延长服用至 10 年。

2013 版《指南》根据 EBCTCG 研究结果<sup>[5]</sup>,将卵巢功能抑制(ovarian function suppression, OFS)放在辅助治疗可选的药物中,但基于 ABCSG-12 研究的结果<sup>[6]</sup>,尚无充分证据显示芳香化酶抑制剂(aromatase inhibitor, AI)联合 OFS 优于 TAM 联合 OFS。SOFT 和 TEXT 两项随机临床试验提供了新的

循证医学依据,其联合分析显示,OFS 联合 AI 组治疗 5 年后 DFS 为 91.1%,明显高于 OFS 联合 TAM 组的 87.3% ( $HR$  0.72; 95%  $CI$  0.60 ~ 0.85;  $P < 0.001$ ),两组 OS 差异无统计学意义<sup>[7]</sup>。亚组分析提示,具有复发高危因素如淋巴结阳性、肿瘤最大直径  $> 2$  cm(化疗亚组)的患者,OFS+AI 较 OFS+TAM 的绝对获益更高。该研究验证了 OFS,尤其是 OFS+AI,在高危患者辅助治疗中的地位和作用。2015 版《指南》将 OFS+AI、OFS+TAM 和 TAM 纳入了绝经前乳腺癌辅助治疗方案,在选择方案时须兼顾两个方面:肿瘤方面,复发风险高或需要辅助化疗;患者方面,相对年轻( $< 35$  岁)、在完成辅助化疗后仍未绝经的病例。同时基于目前最佳循证医学证据,推荐 OFS 治疗时间由以往的 2~3 年改为 2~5 年<sup>[2]</sup>。

### 2. 转移后内分泌治疗

由于 AI 在绝经后患者辅助治疗与转移后一线治疗中的广泛应用,针对晚期乳腺癌内分泌治疗的研究已经进入“后 AI 时代”。基于 BOLERO-2<sup>[8]</sup>、FIRST<sup>[9]</sup> 及 0020<sup>[10]</sup>、0021<sup>[11]</sup> 试验结果,2013 版《指南》建议一类 AI 治疗失败患者可选用另外一类 AI(加或不加依维莫司)或氟维司群(500 mg 或 250 mg)<sup>[12]</sup>。在此基础上,CONFIRM 研究结果显示氟维司群 500 mg 较 250 mg 能显著延长绝经后晚期 HR 阳性患者的无进展生存期(progression-free survival, PFS)( $HR$  0.80)与 OS( $HR$  0.81)<sup>[13]</sup>。这一结论也在中国人中得到证实,且亚组分析发现在 AI 治疗亚组,氟维司群 500 mg 组较 250 mg 组 PFS 延长 1 倍<sup>[14]</sup>。因此,2015 版《指南》着重强调了氟维司群 500 mg 在 AI 治疗失败患者中的临床优势。

### 3. 卵巢保护问题

卵巢早衰是化疗的一种常见不良反应,是化疗药物对女性卵巢不可逆的损害。POEMS 临床试验旨在评估 ER/PR 均阴性的绝经前乳腺癌患者辅助化疗中联合 OFS 能否降低卵巢早衰的发生率<sup>[15]</sup>。结果证明通过药物去势保护卵巢,确实改善了患者的月经功能、生育能力,使患者拥有更好的生活质量及预后改善。因此,2015 版《指南》指出 HR 阴性的绝经前患者在辅助化疗期间使用 OFS 药物可以保护患者的卵巢功能,并且不影响疗效和预后。

### 二、抗 HER-2 分子靶向药物的治疗策略

抗 HER-2 分子靶向药物的出现极大改善了 HER-2 阳性乳腺癌的预后。基于现有循证医学证据,指南对如何合理使用抗 HER-2 靶向治疗药物进行了详细的阐述。

### 1. 标准 HER-2 检测和结果判定

参照美国临床肿瘤学会/美国病理学家学会 2013 版 HER-2 检测指南<sup>[16]</sup> 及中国《乳腺癌 HER-2 检测指南(2014 版)》<sup>[17]</sup>,2015 版《指南》中 HER-2 阳性的标准为免疫组织化学(+++)或原位杂交法(in situ hybridization, ISH)测到 HER-2 基因扩增,即 HER-2/CEP(chromosome enumeration probe)17 比值  $\geq 2.0$  或 HER-2 基因拷贝数  $\geq 6$ ,HER-2 基因拷贝数 4~6 定义为“无法判读”。由于基因扩增与染色体拷贝数增加可能引起 HER-2 表达增加,当存在染色体拷贝数增加时,即使 HER-2/CEP17 比值  $< 2.0$  也判定为阳性。

### 2. HER-2 阳性复发转移乳腺癌治疗原则

HER-2 阳性晚期复发转移乳腺癌首选含曲妥珠单抗克隆抗体为基础的治疗,曲妥珠单抗克隆抗体与化疗药物联用效果优于单纯化疗。基于 H0648g 研究及 M77001 3 期临床研究结果,2013 版《指南》将曲妥珠单抗克隆抗体联合紫杉类药物作为 HER-2 阳性晚期乳腺癌一线治疗<sup>[12,18-19]</sup>。

CLEOPATRA 研究证明在紫杉类联合曲妥珠单抗克隆抗体的标准治疗方案中加入帕妥珠单抗克隆抗体可进一步延长 PFS 和 OS(18.5 个月比 12.4 个月,  $P < 0.001$ ; 56.5 个月比 40.8 个月,  $P = 0.0002$ )且不增加心脏毒性的风险<sup>[20-22]</sup>。该方案迅速被 NCCN 指南收录为 HER-2 阳性转移性乳腺癌的一线治疗首选方案<sup>[23]</sup>。由于帕妥珠单抗克隆抗体尚未在中国内地上市,在帕妥珠单抗克隆抗体无法获得的情况下,2015 版《指南》建议紫杉醇或多西他赛联合曲妥珠单抗克隆抗体作为首选的一线方案,在紫杉醇基础上联用卡铂可以进一步提高疗效<sup>[24]</sup>。对于紫杉类药物耐药或无法耐受的患者,曲妥珠单抗克隆抗体联合长春瑞滨、卡培他滨等化疗药物也可用于一线治疗<sup>[25-26]</sup>。

近年来,抗 HER-2 药物治疗领域最受瞩目的新药即 T-DM1 对既往接受过曲妥珠单抗克隆抗体治疗的 HER-2 阳性乳腺癌患者具有良好疗效。EMILIA 试验是在经曲妥珠单抗克隆抗体治疗后病情进展的 HER-2 阳性乳腺癌中进行的 3 期临床试验,对比了 T-DM1 与拉帕替尼联合卡培他滨方案的疗效与安全性。结果显示 T-DM1 可显著延长 PFS(独立评估: 9.6 个月比 6.4 个月)与 OS(30.9 个月比 25.1 个月),降低了 32% 的死亡风险( $HR$  0.68; 95%  $CI$  0.55 ~ 0.85;  $P < 0.001$ )<sup>[27]</sup>。NCCN 指南将 T-DM1 作为既往接受过曲妥珠单抗克隆抗体治疗的 HER-2 阳性乳腺癌的首选方案<sup>[23]</sup>。





TNBC)能进一步从紫杉醇周疗中获益<sup>[47]</sup>。

提高疗效的另一途径是不断探索新的药物方案,如在化疗方案中联合铂类的疗效。两项大型随机 2 期临床试验 GeparSixto 与 CALGB 40603 均证实 TNBC 新辅助治疗中加入卡铂可以显著提高 pCR 率<sup>[48-49]</sup>。但近期公布的随访数据却不尽如人意: GeparSixto 试验进一步证实卡铂的加入能显著延长 TNBC 患者的 DFS, 而 CALGB 40603 试验中尽管 pCR 率明显增高,但含卡铂新辅助方案未能为 TNBC 患者带来生存获益<sup>[50-51]</sup>。铂类在早期 TNBC 治疗中的地位尚存争议,因此,2015 版《指南》新辅助化疗推荐方案中并未突出铂类的地位,仅在其他化疗方案中提及。

但是基于最新循证医学结果,2015 版《指南》认可了铂类在晚期 TNBC 中的疗效。O'Shaughnessy 等<sup>[52]</sup>发起的 BSI-201 研究中吉西他滨联合卡铂(GC)在晚期 TNBC 展现出良好的疗效与耐受性(PFS 4.1 个月,OS 11.1 个月),使得 NCCN 指南最终将 GC 方案纳入转移性乳腺癌联合治疗推荐方案之一。胡夕春等<sup>[53]</sup>对比了吉西他滨联合顺铂(GP)与吉西他滨联合紫杉醇(GT)方案的疗效,结果显示 GP 方案一线治疗晚期 TNBC 可使肿瘤进展风险降低 31% (PFS 7.73 个月对 6.47 个月;HR 0.69,  $P=0.009$ )。该项研究得到了国内外专家的广泛认可,GP 方案成为 TNBC 转移一线化疗的新选择。2015 版《指南》推荐 TNBC 可选择吉西他滨加卡铂或顺铂。一项进一步比较上述两种含铂方案 GP 与 GC 一线治疗晚期 TNBC 的疗效与安全性的临床试验目前正在进行中,将为肿瘤科医师的临床决策提供更多循证医学证据。

#### 四、骨改良药物的临床应用

双膦酸盐(包括唑来膦酸、伊班膦酸、帕米膦酸二钠)和地诺单抗克隆抗体可以有效治疗乳腺癌的骨转移,并预防乳腺癌骨转移患者发生骨相关事件(skeletal-related events, SREs)。因此,《指南》建议确诊乳腺癌骨转移的患者,满足预期的生存期 $\geq 3$ 个月且肌酐低于 3.0 mg/dl (1 mg/dl = 88.41  $\mu$ mol/L),应在行化疗与内分泌治疗的同时及时予以双膦酸盐或地诺单抗克隆抗体治疗。

双膦酸盐治疗乳腺癌骨转移患者的最佳用药间隔时间是目前研究的热点。一项 3 期临床试验比较了唑来膦酸每 12 周用药与目前标准的每 4 周用药两种给药方案,结果显示每 12 周间隔用药并不会降低唑来膦酸的疗效,两组 SREs 的发生率分别为 23.2% (12 周方案)与 22% (4 周方案)<sup>[54]</sup>。目前

2015 版《指南》推荐的治疗模式为每 4 周 1 次,持续 1 年,后改为每 12 周一次持续治疗。

关于骨改良药物治疗的最佳持续时间目前尚无定论:双膦酸盐使用时间多为 2 年,超过 2 年的长期安全性数据非常有限<sup>[55-57]</sup>,延长使用时间可能会增加获益,但尚未得到证实。因此,2015 版《指南》并未对双膦酸盐用药持续时间做出明确指示。

地诺单抗克隆抗体是一种新型的骨改良药物。一项随机临床试验结果显示,地诺单抗克隆抗体组首次和后续 SREs 时间均显著优于唑来膦酸组 ( $P=0.001$ ),且较唑来膦酸耐受性更好<sup>[58]</sup>。地诺单抗克隆抗体因此被纳入 NCCN 临床指南,但目前地诺单抗克隆抗体的远期毒性尚不明确,其最佳治疗模式还有待探索。

以上为笔者对 2015 版《指南》药物治疗策略更新的解读,希望其有助于临床医师更好的理解和掌握《指南》的变更及其所对应的循证医学证据。笔者相信随着《指南》的发布与不断的更新,中国乳腺癌的诊治将逐渐走向规范化的道路,使更多的乳腺癌患者获益。

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