·综述与讲座·

乳腺癌新辅助内分泌治疗最新研究进展

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［摘要］ 新辅助内分泌治疗在激素受体阳性乳腺癌中应用，可使肿瘤降期、提高手术切除率。围绕乳腺癌新辅助内分泌治疗适宜人群，最佳疗程，与新辅助化疗、新辅助内分泌治疗药物间的疗效的对比，新辅助内分泌治疗疗效评价及预测，生物标志物等方面展开阐述，探讨目前乳腺癌新辅助内分泌治疗研究中的问题及发展趋势。

［关键词］ 乳腺癌；新辅助治疗；内分泌治疗

［中图分类号］ R737.9 ［文献标识码］ A DOI：10.12019/j.issn.1671-5144.2016.02.015

The Recent Development of Research for Breast Cancer Neoadjuvant Endocrine Therapy

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Abstract: Neoadjuvant endocrine therapy, a considerable treatment for hormone receptor-positive patients, can achieve the purpose of downsizing primary tumors and a high operability. This article consists of several parts: Selective patients, treatment duration, neoadjuvant chemotherapy vs. endocrine therapy, assessment of efficacy and possible predictive biomarkers etc. Results from present clinical trials will contribute to future investigation to establish the optimized treatments in individual patients.

Key words: breast cancer; neoadjuvant therapy; endocrine therapy

最近几年，乳腺癌新辅助治疗的研究持续升温。新辅助治疗可使肿瘤缩小降期，提高保乳率，减少手术范围，明确肿瘤生物学特性及对治疗的反应率。对于不适合化疗或者手术的激素受体（hormone receptor，HR）阳性乳腺癌患者来说，新辅助内分泌治疗是一个合适的选择。新辅助内分泌治疗不良反应轻，患者耐受性好，许多临床研究表明新辅助内分泌治疗在选择性乳腺癌患者中应用是安全有效的。

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1 新辅助内分泌治疗适宜人群

HR阳性乳腺癌患者新辅助内分泌治疗可缩小肿瘤，减少手术范围，提高保乳率，毒性更低，患者更容易耐受。新辅助内分泌治疗最初应用于不适合化疗和手术、机体状况不良的老年乳腺癌患者[1-2]。几个大型新辅助内分泌治疗临床研究（P024试验[3]、PROACT试验[4]、IMPACT试验[5]和ACOSOG Z1031试验[6]）入组的患者主要为绝经后HR阳性乳腺癌患者。对于绝经前的乳腺癌患者，新辅助内分泌治疗正在探索阶段。Barbie等的研究表明，HR阳性乳腺癌患者，新辅助内分泌治疗对绝经前和绝经后乳腺癌的治疗反应是相似的[7]。2015年的圣加仑会议共识[8]指出：Luminal

A型乳腺癌患者对化疗不敏感，专家普遍不建议行新辅助化疗，只有在保乳手术不能实施的情况下考虑新辅助化疗，对于内分泌治疗敏感的绝经后患者，新辅助内分泌治疗是合理有效的。

2 新辅助内分泌治疗适宜疗程

芳香化酶抑制剂（aromatase inhibitor，AI）新辅助内分泌治疗临床试验表明经过3~12个月的治疗，客观缓解率为40%~80%，5%~10%的患者出现早期进展性疾病[9]。总的来说50%~90%的患者经过AI内分泌治疗后适合保乳手术。AI新辅助内分泌治疗6个月、8个月或12个月疗程的疗效均优于4个月[10-12]。许多新辅助内分泌治疗试验，术前给予患者3~4个月的内分泌治疗。Dixon等的一项临床研究纳入绝经后女性乳腺癌患者（中位年龄78岁），可手术局部晚期雌激素受体（estrogen receptor，ER）阳性患者给予3个月及以上的来曲唑新辅助内分泌治疗[13]。3个月后，182例中63例继续内分泌治疗，肿瘤体积进一步缩小，与3个月疗程相比反应率提高（83.5% vs. 69.8%），保乳率提高（72% vs. 60%）。由Llombart-Cussac等[14]实施的Ⅱ期临床试验表明新辅助内分泌治疗达到临床反应的中位时间为3.9个月，最大临床疗效中位疗程时间为4.2个月，三分之一患者治疗最大化时间超过6个月，该试验表明4~6个月新辅助内分泌治疗可评估疗效，个体化的治疗时间更适合提高疗效。2015年的圣加仑会议共识[8]指出：新辅助内分泌治疗是根据疗效、不良反应及并发症综合评估进行的个体化治疗。大多数专家建议应该持续4~8个月或至治疗反应最大化。

3 新辅助内分泌治疗效果的评估

过去，新辅助治疗期间抗肿瘤效果通过乳腺钼靶和B超来监测。相比CT和PET，乳腺MRI应用越来越广泛，这些监测手段假阳性率和假阴性率仍然存在。需联合几种评估方法平行评价新辅助治疗抗肿瘤疗效来决定个体手术的最佳时间窗。

新辅助治疗可以提高保乳率，可以用来评估预后，对肿瘤起疗效预示着长的无病生存期。在局部晚期乳腺癌新辅助治疗后抗肿瘤效果的病理学评估已成为重要手段[15]。新辅助内分泌治疗后有病理性变化[病理完全缓解（pathologic complete response，pCR）和病理部分缓解（pathologic partial response，pPR）]与无变化患者的无病生存期比较差异有统计学意义[16]，预后优于无变化患者。美国食品药品监督管理局（Food and Drug Administration，FDA）提出，pCR可以合理预测临床获益，因此可用来评估新辅助治疗的疗效。一项荟萃分析表明[17]，pCR不能替代乳腺癌的无病生存率（disease-free survival，DFS）和总生存率（overall survival，OS）作为治疗终点。然而pCR可以作为特定治疗方案如剂量密集方案以及特定类型乳腺癌治疗如三阴性乳腺癌及人类表皮生长因子受体2（human epithelial growth factor receptor 2，HER2）阳性型乳腺癌的疗效评估。pCR是新辅助化疗追求的目的，但在HR阳性的患者中，pCR率低，仅有2%~10%[18-19]。因此需要其他病理学评分系统评估新辅助内分泌治疗的效果。

4 化疗vs.内分泌治疗

4项研究比较新辅助化疗与内分泌治疗的疗效[20-23]，新辅助内分泌治疗和新辅助化疗临床反应率分别为48%~89% 和64%~85%，其中3项研究入组患者仅为HR阳性患者[20-22]，其中Semiglazov等的临床研究入组239例绝经后HR阳性患者，该临床试验表明：新辅助内分泌治疗（AI）的疗效[客观缓解率（overall response rate，ORR）和保乳率]至少与新辅助化疗相当[22]。另外Alba等的95例HR阳性乳腺癌患者的回顾性研究中，新辅助内分泌治疗组和新辅助化疗组临床反应率无显著差异（P=0.075）[20]。

5 新辅助内分泌治疗药物和疗效比较

目前新辅助内分泌治疗的方案主要是他莫昔芬与第三代AI。目前使用的第三代AI主要有三种，分别为非甾体类：阿那曲唑和来曲唑；甾体类：依西美坦。新辅助内分泌治疗临床研究主要集中在他莫昔芬与第三代AI之间的疗效对比。

5.1 绝经后患者新辅助内分泌治疗药物和疗效比较

5.1.1 阿那曲唑vs.他莫昔芬

两项大型临床Ⅲ期试验比较阿那曲唑和他莫昔芬新辅助内分泌治疗的疗效，分别是PROACT试验[4]和IMPACT试验[5]。

PROACT试验是一项随机多中心研究，比较阿那曲唑1.0 mg和他莫昔芬20 mg的疗效，入组绝经后HR阳性肿瘤体积较大可手术或者有手术可能的患者（T2/T3/T4，N0-2，M0）。451名患者随机分到他莫昔芬组（n=223）和阿那曲唑组（n=228），疗程为期3个月。此试验允许加用化疗。该试验主要终点指

标是3个月后新辅助治疗的ORR。阿那曲唑和他莫昔芬的ORR分别为39.5%和35.4%（乳腺彩超，*P*=0.29）、50%和46.2%（卡钳测量，*P*=0.37）。在单纯内分泌治疗组（n=314），43%的阿那曲唑组患者可手术率提高了，他莫昔芬组为30.8%（*P*=0.04）。在意向治疗组，阿那曲唑组可手术率数值上优于他莫昔芬组，尽管未达到统计学意义上的差异。该研究指出阿那曲唑的疗效至少和他莫昔芬相当。

IMPACT试验设计：临床或者生物学疗效方面，绝经后ER阳性乳腺癌患者应用新辅助内分泌治疗，他莫昔芬与阿那曲唑或者二者联合进行比较。该试验入组绝经后可手术的局部晚期乳腺癌患者（locally advanced breast cancer，LABC）进行随机双盲试验，按照1∶1∶1比例，阿那曲唑组（n=113）1.0 mg/d，他莫昔芬组（n=108）20 mg/d，阿那曲唑组1.0 mg/d+他莫昔芬20 mg/d组（n=109），术前为期3个月。用卡尺测量和乳腺彩超评估ORR。结果表明该试验三个试验组的ORR没有显著差异。试验组中HER2阳性乳腺癌（n=34），阿那曲唑组ORR优于他莫昔芬（58% vs. 22%，*P*=0.18），该试验表明ER阳性绝经后乳腺癌患者阿那曲唑新辅助内分泌治疗的疗效和耐受性与他莫昔芬相当。

5.1.2 来曲唑vs.他莫昔芬

许多临床试验使用来曲唑作为新辅助内分泌的治疗药物。P024试验[3]是一项大型Ⅲ期随机双盲多中心临床试验，比较来曲唑和他莫昔芬的疗效。入组337例绝经后HR阳性初治患者。分为来曲唑组和他莫昔芬组，每日分别给予来曲唑2.5 mg和他莫昔芬20 mg，疗程为期4个月。该试验的主要终点指标为临床检查评估比较总的ORR［ORR=完全缓解（complete response，CR）+部分缓解（partial response，PR）］，次要终点指标为超声或钼靶评估ORR和保乳率。ORR来曲唑组vs.他莫昔芬组分别为：临床触诊55% vs. 36%，*P*≤0.001，超声35% vs. 25%，*P*=0.042，钼靶34% vs. 16%，*P*≤0.001，保乳率比较分别为45%和35%（*P*=0.022）。该试验表明，绝经后HR阳性乳腺癌患者中，新辅助内分泌治疗来曲唑的疗效优于他莫昔芬。患者对来曲唑的耐受性与他莫昔芬相当。

5.1.3 依西美坦

依西美坦是唯一的甾体类AI应用于乳腺癌的治疗。依西美坦表现出与非甾体类不同的药理作用。依西美坦已经被用于一些小型的单组临床新辅助内分泌治疗试验[24-28]，这些试验表明依西美坦是安全有效的，临床反应率25%~70%。

5.1.4 阿那曲唑、来曲唑和依西美坦三者比较

ACOSOG Z1031试验[6]是一项前瞻性试验，比较依西美坦、阿那曲唑和来曲唑三种药物4个月新辅助内分泌治疗的疗效差异。研究发现来曲唑反应率最高（74.8%），依西美坦和阿那曲唑无显著差异（62.9%和69.1%），三个试验组治疗前保乳率分别是52%、50%和57.7%。治疗后三组保乳率无显著差异（60.8%、67.8%和77%）。

5.2 绝经前患者新辅助内分泌治疗药物及疗效比较

AI在绝经后女性患者中是有效和耐受的[3]。AI新辅助内分泌治疗在绝经前女性患者中的临床应用数据有限。

Torrisi等[29]分析了来曲唑+卵巢功能抑制（促黄体激素释放激素类似物）的疗效，来曲唑治疗中位治疗时间5.2个月。32名患者临床获益。其中1名（3%）患者达到临床CR及pCR。15名（47%）患者达到部分缓解（ORR=50%）。另外Torrisi实施的非随机化试验中，来曲唑+促黄体激素释放激素类似物+新辅助化疗在绝经前局部晚期乳腺癌患者中应用有效改善了DFS[30]。

Masuda等实施的绝经前患者新辅助内分泌研究[31]——STAGE试验，随机入组204例ER阳性、HER2阴性绝经前女性乳腺癌患者，随机分成戈舍瑞林+他莫昔芬组和戈舍瑞林+阿那曲唑组，术前给予6个月的戈舍瑞林+阿那曲唑或者他莫昔芬。研究发现阿那曲唑组相对他莫昔芬组ORR更高（70.4% vs. 50.5%，*P*=0.004）。相似地，超声和MRI疗效评估阿那曲唑组同样明显优于他莫昔芬组。

6 生物学标志物预测内分泌治疗疗效

生物学标志物对于新辅助治疗的乳腺癌患者具有预测疗效的价值，其中包括HR表达水平[5,32-33]，肿瘤组织学分级[34]，组织类型[18]和增值指数如Ki-67[35]等。

两大在绝经后ER阳性乳腺癌患者展开的随机新辅助内分泌试验IMPACT试验及Ellis等的Ⅲ期临床试验结果支持ER表达水平与新辅助内分泌治疗反应率有关[5,32]。ER高表达患者新辅助内分泌治疗反应率也高[5,32]。ER表达水平越高，新辅助内分泌治疗后2周和12周后Ki-67下降水平也明显[35]。另外，ER和孕激素受体（progesterone receptor，PR）与新辅助化疗反应率也可能有关联。Colleoni等回

顾性分析553例乳腺癌患者新辅助化疗后内分泌治疗高反应率的患者(ER和PR≥50%),未出现pCR;ER或PR(0~49%)患者中pCR 3.3%;HR阴性患者pCR可达17.7%($P<0.000\ 1$)[33]。

新辅助治疗前,局部晚期乳腺癌患者Ki-67测定预测化疗疗效。大数据回顾性研究指出,多变量分析中,Ki-67基线水平高是预示pCR的独立因素[34,36]。新辅助化疗后Ki-67的表达水平与预后有关,新辅助化疗后Ki-67表达水平越高,无病生存越差[37-38]。近期临床研究表明,Ki-67可预测ER阳性乳腺癌患者新辅助内分泌治疗疗效。新辅助内分泌治疗后Ki-67水平可作为治疗疗效的标志物,具有重要的预后评估价值。新辅助内分泌治疗后的PEPI评分(术前内分泌治疗预后指数preoperative endocrine therapy prognosis index)可以有效评估HR阳性乳腺癌患者个体内分泌治疗反应,可以使一部分患者术后免于化疗。IMPACT试验[5],淋巴结阴性、PEPI评分为0的患者(低Ki-67表达水平和ER高表达)无复发[39]。

显然,每个独立临床病理部门检验结果的一致性、可重复是非常重要的。ER、PR和Ki-67测定必须要有统一的指南。

乳腺癌基因检测已被运用于新辅助治疗反应率的预测[40]。基因检测包括扩增基因、ER、PR、调控基因,如21基因检测等,复发风险评分也许更具预测价值。比起免疫组化,基因检测更具准确性。ER阳性乳腺癌中,PAM50分型分析可以区分出适合新辅助内分泌治疗的患者,可排除非Luminal类型内分泌抵抗肿瘤[6]。然而,对大多数患者进行基因检测是难以实施的。目前,ER阳性乳腺癌基因检测仍然是不足以区分哪些患者可免于化疗,哪些患者化疗后可达到pCR。而免疫组化的检测相比基因检测更容易推广[41]。Luminal A型乳腺癌(ER阳性/PR阳性,HER2阴性,Ki-67≤14%)也许是非常适用新辅助治疗的乳腺癌亚型,但是Luminal A型未被常规用于新辅助治疗研究的入组患者的标准。

7 问题与展望

新辅助内分泌治疗和化疗都能起到肿瘤降期提高保乳率的作用。对于HR阳性低复发风险的乳腺癌患者,新辅助内分泌治疗与化疗疗效相当,患者更容易耐受,因此新辅助内分泌治疗对于不适化疗、HR阳性乳腺癌患者来说不失为理想的选择。多项研究越来越清楚地表明AI比他莫昔芬更具优越性,尤其对于绝经后的乳腺癌患者。更长疗程新辅助内分泌治疗似乎更能实现更高临床反应率并提高保乳率。新辅助内分泌治疗的最合适人群,最佳药物选择或搭配,最佳治疗疗程,与靶向药物联合,新辅助内分泌药物耐药,可靠疗效预测因子等一系列问题仍有待进一步探索。中国乳腺癌患者发病于绝经前的妇女较多,目前新辅助内分泌治疗临床研究主要集中在绝经后患者,绝经前新辅助内分泌治疗是否和绝经后患者一样起到相当的疗效,仍有待进一步探索。

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[收稿日期] 2015-12-01