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Targeted Therapy in Breast Cancer: highlights from ASCO 2009

Shou-ching Tang (唐守清)

Metastatic breast cancer (MBC) is an incurable disease. The medium survival of MBC is 2 — 3 years with the aim of treatment focusing on symptom control and quality of life (QOL). Despite the availability of many new drugs, the overall survival (OS) of MBC has not changed significantly for the past decades. The clinical research of MBC has been focused on the development of targeted cytotoxic or biological therapy that will increase the therapeutic ratio to increase the efficacy and decrease the toxicity in MBC. The utility of targeted therapy depends largely on the identification and validation of molecular markers that will be prognostic to risk stratify patients in order to offer more aggressive therapy (prognostic marker) or predictive in order to select specific therapy (predictive marker). At the ASCO 2009, many prognostic markers have been validated or revalidated including the MammaPrint, uPA/PAI-1, PARP-1, HER-2 and VEGF, while SPARC, TOP2α and CYP2D6 warranted further investigation. Over-expression of RAD51, a DNA repair gene, was found to be associated with increased risk of LRR and death in locally advanced breast cancer, while sereum Vit D was not prognostic in postmeno-pausal breast cancer patients. Fibroblast growth factor receptor-4 Gky388Arg polymorphism was found to associate with response to AC-D in EBC. Correlation of Akt phosphorylation at Ser473 was made with the benefit from paclitaxel following AC in NSABP B-28. PIK3CA mutation predicted favorable outcome in luminal B [ER (+) and HER-2 (+)]BC. Anti-EpCAM (adhesion molecule) predicted response with docetaxel in refractory MBC.

The real excitement of ASCO 2009 centered around a new group of drugs called PARP inhibitors. BRCA1/2 and PARP-1 are involved in DNA

作者单位:University of Colorado, USA (美国科罗拉多大学)

damage repair in normal cells. Cells deficient in BRCA1/2 depend on PARP-1 for DNA repair. Targeted therapy against PARP was found to be highly active in selected patient population such as triple negative breast cancer when added to gemcitabine and carboplatin or tumor with BRCA1/2 mutation when used alone after failing many prior therapies. PARP-1 inhibitors (BSI-201 and olaparib) selectively kills BRAC1/2 deficient cells. Accumulated single-strand DNA breaks are converted to double-stand breaks during DNA replication, causing the collapse of replication forks. These studies provided the proof of concept in the drug design. Many investigators wondered if a planned phase III study to combine the PARP inhibitors with chemotherapy such as gemcitabine and carboplatin is really necessary in the unique patient population where limited treatment options are available.

RIBBON I was a phase III trial of chemotherapy +/− bevasizumab (B) in the first line treatment of MBC. The addition of B increased progression free survival (PFS) and response rate (RR) but not OS. The concept of combination versus single sequential chemotherapy was explored together with the role of maintenance chemotherapy. The results reinforced our current clinical practice guideline in MBC. Finally, the addition of ixabepelone to B in MBC was found to be well tolerated.

The identification of prognostic and predictive markers in early breast cancer is even more important. Of the validated markers, HER-2 amplification is the most presented. HER-2 (+) tumor benefited from trastuzumab in the adjuvant setting, regardless of clinical/pathological features. Several HER-2-targeted agents were shown to be active after progression on trastuzumab in metastatic setting, and are synergistic and/or additive with trastuzumab. T-DM1 (anti-microtubule agent) was found to be high active in patients who progressed on trastuzumab. Neratinib (oral pan-ErB TKI) with trastuzumab has activity in patients progressed on trastuzumab. Pertuzumab (binds to dimerization domain of HER-2) and trastuzumab has higher activity than either alone. BIBW 2992 (oral dual EGFR/HER-2 inhibitor) has activity on progression with trastuzumab.

The I-Spy study investigated the predictive markers for response to neoadjuvant chemotherapy. Response was assessed by serial MRI, complete

pathological response (pCR) and residual cancer burden (RCB). The study identified low score of MammaPrint, Oncotype DX, luminal A and favorable ER/HER-2 to predict a lack of benefit from the chemotherapy while high score of p4BP1, eNOS, cAb1, STAT 5, EGFR and AKT predicted pCR from the treatment. The Neo-tAnGo trial explored the sequencing of anthracyclines/taxanes with or without gemcitabine in locally advanced breast cancer (LABC). While the epirubicin/cyclo-phosphamide (EC) followed by paclitaxel (P) or paclitaxel/gemcitabine (PG) resulted similar pCR, PG followed by EC was found to be superior than the reverse sequencing, EC followed by PG. This study provided yet another evidence that taxanes prior to anthracyclines may be better than the current standard approach of taxanes following anthracyclines in the adjuvant setting.

A large Japanese study compared the standard adjuvant anthracyclines/taxanes with that of taxane alone in early breast cancer, without testing HER-2 or trastuzumab treatment. Patients randomized to taxane-alone arm had a similar even-free survival supporting the concept that taxanes may safely replace anthracycline in the adjuvant treatment of early breast cancer. In a sub-group analysis, patients whose tumor over-expressed HER-2 did better with the anthracyline treatment. Consistently in a retrospective analysis of the Canadian MA 5 adjuvant trial comparing CMF and CEF, patients whose tumor did not amplify HER-2 (triple negative) actually had shorter survival when treated with the anthracycline-based chemotherapy CEF. Both studies added further evidence that the target of anthracyclines indeed included topoisomerase II which is co-amplified with HER-2. In a retrospective analysis of the switching trials from tamoxifen to aromatase inhibitors in the adjuvant setting, the presence of progesterone receptor (PR) predicted benefit from the prolonged tamoxifen treatment.

Finally, several interesting adjuvant radiation questions were addressed. The MIRROR study explored the benefit of axillary treatment with either complete dissection (cALND) or radiation (axRT) in patients with micrometatasis from the sentinel lymph node dissections. The study identified macro-metastasis (pN_{1mi}) as a high risk factor that warrant further cALND or axRT while micro-metastasis [pN_0(i+)] may require

further treatment depending on other prognostic factors. A retrospective study in patients with 1—3 positive axillary lymph node metastasis recommended axRT since these patients were found to have increased risk of relapse without the therapy. Lastly, a meta-analysis of 3 randomized trials provided the evidence that partial breast radiation was as effective as that of whole breast radiation for overall and distant even-free survival with decreased morbidity, although with increased locoregional relapse.

In summary, the prognostic and/or predictive markers help to indentify a sub-group of patients to offer individualized treatment. Many markers and targets were validated or further validated from ASCO 2009, including MammaPrint, uPA/PAI-1, PARP-1, HER-2 and VEGF. Further studies are needed for SPARC, TOP2α and CYP2D6. Targeted therapy against PARP is highly active in selected patient population. HER-2(+) tumor benefit from trastuzumab, regardless of clinical/pathological features. Several HER-2-targeted agents are active after progression on trastuzumab, and are synergistic/additive with trastuzumab. Taxane followed by anthracycline may be better than the traditional sequence in EBC. Bevacizumab increases PFS in combination with capecitabine as well as taxanes. Single sequential therapy with chem-otherapy holiday does not decrease survival and offers better QOL.

译文：

ASCO 2009年会有关乳腺癌靶向治疗的亮点

转移性乳腺癌(MBC)的存活时间一般为2～3年，其治疗主要以改善症状及提高生活质量为目的。过去几十年里，尽管许多新药对转移性乳腺癌有一定效果，但其总生存率却提高不明显。转移性乳腺癌的临床研究一度致力于研发细胞毒或生物制剂以提高治疗比率，进而提高药效且降低毒性。有效的靶向治疗主要依赖于预后因子或疗效预测因子的确定，然后根据各因子特点将患者分类给予特定的治疗。美国临床肿瘤学会(ASCO)2009年会上，许多预后因子被证实或再次确认，包括MammaPrint、uPA/PAI-1、聚ADP核糖聚合酶1(PARP-1)、HER-2及血管内皮生长因子(VEGF)，而富含半胱氨酸的酸性分泌蛋白(SPARC)、拓扑异构酶Ⅱα(TOP2α)、CYP2D6则需进一步研

究。新的研究发现:DNA 修复基因(RAD51)过表达与局部晚期乳腺癌局部复发率及死亡率高密切相关;而血清 VitD 并不是绝经后乳腺癌患者的预后因素。成纤维细胞生长因子受体-4 G388A(FGFR-4 Gky388Arg)基因多态性与早期乳腺癌患者采用多柔比星、环磷酰胺序贯多西紫杉醇(AC-D)化疗的疗效相关。NSABP B-28 研究显示,丝氨酸-苏氨酸蛋白激酶 473 位点磷酸化(p-Akt-Ser^473)与多柔比星、环磷酰胺序贯紫杉醇(AC-P)化疗的受益相关。磷脂酰肌醇 3 激酶(phosphatidylinositol 3-kinase,PIK3CA)突变预示 luminal B 型[ER(+)和 HER-2(+)]乳腺癌预后较好,上皮细胞黏附分子抗体(Anti-EpCAM)表达可预测多西他赛治疗难治性 MBC 的疗效。

ASCO2009 年会的焦点与一组名为 PARP 抑制剂的药物相关。BRCA1/2 和 PARP-1 参与正常细胞 DNA 损伤的修复,BRCA1/2 缺失的细胞则依赖 PRAP-1 进行 DNA 的损伤修复。研究发现,针对 PRAP 的靶向治疗药物可与吉西他滨、卡培他滨联用治疗三阴性乳腺癌或单独用于经多种治疗失败的 BRCA1/2 突变的乳腺癌,其疗效均高度有效。PARP-1 抑制剂(BSI-201 和 Olaparib)选择性杀死 BRCA1/2 缺失的细胞。累积的 DNA 单链断裂在 DNA 复制时转变为 DNA 双链断裂,导致复制叉瓦解。这些研究为该药的研发提供了理论依据。许多研究者想知道:有关 PARP 抑制剂联合化疗(如吉西他滨、卡培他滨)用于治疗手段有限的特定患者群体的Ⅲ期研究是否必要。

RIBBON Ⅰ研究是探讨化疗联合或不联合贝伐单克隆抗体(B)用于 MBC 一线治疗的Ⅲ期研究。研究表明,加用贝伐单克隆抗体可提高无疾病进展生存(PFS)率和有效率(RR),但却不能提高总生存率(OS)。研究还比较了联合化疗与单药序贯化疗以及维持化疗的疗效,结果支持目前临床治疗 MBC 的实践指南。贝伐单克隆抗体加用伊沙匹隆(ixabepelone)治疗 MBC,患者耐受性良好。

确定早期乳腺癌预后因子及疗效预测因子也相当重要。所有有效因子中,HER-2 基因的扩增最常见。HER-2(+)肿瘤可从曲妥珠单克隆抗体治疗中受益,而不用考虑其他临床或病理因素。曲妥珠单克隆抗体治疗转移性乳腺癌期间发生疾病进展的患者,给予其他 HER-2 靶向制剂(单用或与曲妥珠单克隆抗体联用)治疗有效。T-DM1(一种抗微管制剂)对曲妥珠单克隆抗体治疗发生进展的乳腺癌患者有明显疗效。Neratinib(口服的泛 ErbB 类酪氨酸激酶抑制剂)联合曲妥珠单克隆抗体对曲妥珠单克隆抗体治疗失败患者有效。帕妥珠单克隆抗体(与 HER-2 受体胞外结构域Ⅱ区结合,抑制二聚体形成)与曲妥珠单克隆抗体联用比两种药物分别单独使用的效果好。BIBW 2992(口服的 EGFR/HER-2 双重抑制剂)对曲妥珠单克隆抗体治疗失败的患者有效。

I-Spy研究探讨了新辅助化疗的疗效预测因子,新辅助化疗疗效通过MRI连续检测、完全病理学缓解(pCR)和残留肿瘤负荷(RCB)进行评估。结果显示,MammaPrint、Oncotype、luminal A和ER(或)HER-2预测化疗效果不佳,而p4BP1、一氧化氮合酶(eNOS)、cAb1、信号传导和转录激活因子5(STAT5)、表皮生长因子受体(EGFR)、AKT对pCR有预测作用。NeotAnGo试验研究了蒽环类与紫杉类(紫杉醇类联合或不联合吉西他滨)的用药顺序对局部晚期乳腺癌患者的疗效影响。结果显示,表柔比星+环磷酰胺(EC方案)序贯紫杉醇(P)治疗与EC序贯紫杉醇+吉西他滨(PG)治疗相比,两组间病理完全缓解率无明显差异;PG序贯EC治疗疗效明显优于EC序贯PG治疗疗效。该研究进一步表明紫杉醇类序贯蒽环类的疗效优于现阶段常规使用的蒽环类序贯紫杉醇类的疗效。

日本一项大型研究比较了标准蒽环类联合紫杉类药物与紫杉类单药治疗早期乳腺癌患者的疗效,没有进行HER-2检测或曲妥珠单克隆抗体治疗。纳入患者随机分组,紫杉类单药组与联合蒽环类组相比,无事件生存(EFS)无显著差异,进一步表明紫杉类可替代蒽环类用于早期乳腺癌的治疗。亚组分析显示,HER-2过表达患者接受蒽环类药物治疗效果较好。加拿大MA 5辅助试验的一项回顾性分析比较了CMF方案和CEF方案疗效,三阴性乳腺癌患者接受蒽环类为主的CEF方案化疗,其生存期较短。以上所有研究表明蒽环类作用的靶点包括拓扑异构酶Ⅱ,而拓扑异构酶Ⅱ与HER-2共同过度表达。一项关于他莫昔芬治疗转为芳香化酶抑制剂治疗的回顾性分析显示,PR阳性患者长期服用他莫昔芬治疗效果好。

最后,会议探讨了关于放射治疗的一些有意义的问题。MIRROR研究分析了经前哨淋巴结活检发现淋巴结微转移的乳腺癌患者行腋窝淋巴结清扫术或全腋窝放射治疗的疗效,结果显示,pN_{1mi}是决定进一步行腋窝淋巴结清扫术或全腋窝放射治疗的高风险因素,而pN_0(i+)患者可根据其他预后因子选择进一步治疗。一项回顾性研究显示,1~3枚腋窝淋巴结转移的患者如不接受局部放射治疗,其复发风险增高,所以建议行全腋窝放射治疗。

对3项随机试验研究的一个meta分析显示,尽管部分乳房照射局部复发率较高,但它与全乳房照射在OS和远期EFS方面无差异。

小结:预后因子和(或)疗效预后因子可以识别一部分患者亚群接受个体化治疗。ASCO 2009年会确认了许多乳腺癌相关的因子及治疗靶点,包括MammaPrint、uPA/PAI-1、PARP-1、HER-2及VEGF,而SPARC、TOP2α、CYP2D6则需进一步研究。针对PARP的靶向治疗对符合该项治疗条件的患者高度有效。HER-2(+)肿瘤患者从曲妥珠单克隆抗体治疗中受益,不必考虑临床或病理因素。一些HER-2靶向治疗药物对曲妥珠单克隆抗体治疗

失败的肿瘤有效,可以序贯或联合曲妥珠单克隆抗体使用。早期乳腺癌治疗中,紫杉醇类序贯蒽环类的治疗效果较常规顺序(蒽环类序贯紫杉醇类)好。贝伐单克隆抗体与卡培他滨以及紫杉醇联用可提高无疾病进展生存率。“休假假说”认为:靶向治疗和化疗可序贯使用,即化疗后疾病进展可改用靶向治疗,靶向治疗失败后再改用原化疗方案,对部分患者是有效的。这种序贯治疗不仅不会缩短生存期并且还可提高生活质量。

【关键词】 乳腺肿瘤;转移;化疗;单克隆抗体;放射治疗

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(王姝姝 翻译 范林军 审校)

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