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REVIEW ARTICLE **CME**

Treatment Horizons for Triple-negative Breast Cancer

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ABSTRACT

Triple-negative breast cancer is a distinct clinical subtype characterised by tumours that do not express oestrogen receptor, progesterone receptor, or HER-2 oncogene. Patients with triple-negative breast cancer have been reported to have a poor outcome. The mainstay of systemic treatment is chemotherapy. It has been noted that triple-negative breast cancer may be further sub-classified and one of the subclasses is the* BRCA*-associated tumour. In this article, systemic treatment for triple-negative breast cancer in the advanced metastatic, neoadjuvant, and adjuvant setting will be discussed. In particular, recent data in relation to the role of platinum compounds and poly (ADP-ribose) polymerase inhibitors will be reviewed.

Key Words: *Platinum; Poly(ADP-ribose) polymerases/antagonists & inhibitors; Triple negative breast neoplasms*

中文摘要

三陰性乳癌的治療端倪

楊明明

三陰性乳癌雌激素受體、孕激素受體及HER2均呈陰性。三陰性乳癌患者預後較差。主要的系統治療方法為化療。三陰性乳癌的亞型可再細分，其中一亞型與*BRCA*基因突變相關。本文將討論轉移性三陰性乳癌的系統治療及誘導化療和輔助化療，並側重討論鉑藥及PARP抑制藥在三陰性乳癌的應用。

INTRODUCTION

Breast cancer is a common disease. According to the Hong Kong Cancer Registry, there were over 3500 new breast cancer cases in 2012.[1] Triple-negative breast cancer (TNBC) is defined as having a negative status for hormone receptors (oestrogen receptor [ER] and progesterone receptor [PR]) and human epidermal growth factor receptor 2 (HER2). Local data indicate that approximately 14% of our breast cancer patients have triple-negative disease.[2]

TNBC is a heterogeneous disease on a molecular level and also on a pathological and clinical level. It is characterised by absence of the common breast cancer therapeutic targets that include those for hormone receptors and HER2 protein overexpression. For this

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reason, both neo/adjuvant systemic treatment and systemic palliative therapy for metastatic TNBC is limited to chemotherapy. Whilst it is known that patients with TNBC have a higher risk of disease relapse, it has also been established that chemotherapy is an effective treatment.[3-6]

The management of patients with TNBC is complicated by the significant molecular heterogeneity that exists within TNBC. Sub-classifications of TNBC based on the presence of biomarkers and gene signatures have identified subclasses that include basal-like tumours, *BRCA*-mutant and BRCAness subtypes, and Claudin-low subtype.[7]

In unselected patients with TNBC, approximately 20% have a *BRCA1* or *BRCA2* mutation, and the incidence increases with a significant family history and younger age.[8] *BRCA* mutation–associated breast cancers are characterised by DNA homologous recombination deficiency (HRD), and 80% of *BRCA1*-associated breast cancers display the basal-like molecular subtype. In sporadic TNBC cases, HRD has been reported via methylation, somatic mutation, and other epigenetic mechanisms. When homologous recombination fails, other DNA repair processes take over driving a mutator phenotype.[9]

METASTATIC SETTING

For metastatic TNBC, interpretation of available data has been hampered by the use of varying definitions of 'triple-negative' in earlier studies. Further, very few studies have focused on TNBC patients, with most reports having been based on subgroup analysis. Data are further hindered by the lack of characterisation of *BRCA1/2* mutations within these trials. The mainstay of current treatment strategies include many chemotherapy agents, such as the anthracyclines, taxanes, ixabepilone, and platinum agents.[7]

BRCA1 and 2 share function in the DNA double-strand break and replication fork damage response.[9] BRCA1 and 2 are involved in the repair of DNA platinum adducts.[10] In-vitro studies have shown that *BRCA1*-mutated basal-like breast cancer has specific sensitivity to cisplatin.[11,12] Preclinical data suggest that TNBCs are more sensitive to platinum compounds that damage DNA inter-strand crosslinking, due to deficiencies in the *BRCA*-associated DNA repair mechanism.[13]

One of the first studies to demonstrate the role of cisplatin in TNBC was reported by Sledge et al,[14] in which five out of eight patients with ER-negative and PR-negative breast cancers responded to cisplatin as first-line therapy for their metastatic disease; in contrast, only one of seven patients with ER-positive and PR-positive breast cancers responded to the same treatment.[14]

Although *BRCA1* mutation carriers appear to benefit from anthracycline-taxane–containing regimens as much as sporadic TNBCs,[15] they have also been shown to be particularly sensitive to platinum compounds. Genomic patterns resembling *BRCA1*- and *BRCA2*-mutated breast cancers have been reported to predict benefit from intensified carboplatin-based chemotherapy.[16] In a study that involved 20 breast cancer patients with germline *BRCA1* mutations, use of platinum resulted in a response rate of 80% and a time-to-progression of 12 months.[15] In the TBCRC009 study, the use of cisplatin or carboplatin provided a response rate of 55% among 11 germline *BRCA* carriers, while the response rate among 75 non-*BRCA* mutant carriers was only 20%.[17] Interestingly, in this latter study, 27 *BRCA1/2* wild-type tumours had been assessed for HRD; among them, five responders had a higher HRD score compared with non-responders.

The TNT study randomised 376 patients with TNBC or *BRCA1/2* breast cancer to either carboplatin or docetaxel in the first-line metastatic setting with a crossover design. The results showed a non-significant difference in response and progression-free survival. However, for BRCA-associated tumours, carboplatin was significantly better than docetaxel in contrast to non–basal-like tumours where the reverse was true.[18]

The role of platinum in TNBC was formally tested in a recently reported phase III study, in which 240 patients were randomly assigned to either cisplatin + gemcitabine or paclitaxel + gemcitabine.[19] After a median follow-up of 16 months, the median progression-free survival was 7.73 months in the cisplatin + gemcitabine group and 6.47 months in the paclitaxel + gemcitabine group (hazard ratio=0.692; p for non-inferiority, <0.0001; p for superiority, 0.009). It has been commented that the paclitaxel schedule adopted in this regimen was suboptimal; that is, it remains unknown whether the cisplatin + gemcitabine regimen would be superior to paclitaxel + gemcitabine if a weekly paclitaxel schedule instead of the 3-weekly paclitaxel schedule was adopted. Nonetheless, based on

the results of this study, cisplatin+gemcitabine provides a non-anthracycline and non-taxane combination regimen that is effective in the first-line setting for patients with metastatic TNBC, and suggests a role for platinum-based therapy in the treatment of TNBC.

In breast cancer, poly(ADP-ribose) polymerase 1 (PARP-1) protein is overexpressed during malignant transformation. It has been associated with higher tumour grade and triple-negative disease with reduced survival. These breast cancer subtypes often harbour dysfunctions in other DNA repair systems, such as BRCA1 and BRCA2. The ability to inhibit PARP-1 using specific inhibitors provides an opportunity to treat these breast cancer subtypes.[20]

PARP inhibitors have been studied among patients with breast cancer and ovarian cancer; tumours that arise in patients with *BRCA* mutations have also been shown to be particularly sensitive to these agents. In a first proof-of-concept study, olaparib, a PARP inhibitor, has demonstrated high response rates among breast cancer patients with germline *BRCA1/2* mutations. In this phase I study, patients with recurrent, advanced breast cancer who had confirmed *BRCA1* or *BRCA2* mutations were treated with olaparib; up to 22% responded to the agent.[21] In contrast to this, Gelmon et al[22] conducted a phase II study to test olaparib in patients with high-grade serous and/or undifferentiated ovarian carcinoma or TNBC. Although the ovarian cancer cohorts confirmed an objective response in seven (41%) of 17 patients with *BRCA1* or *BRCA2* mutations and 11 (24%) of 46 without mutations, there was no confirmed response in patients with breast cancer.[22]

In a phase III study that randomised 590 patients to gemcitabine and carboplatin with or without iniparib (an agent previously considered to be a PARP inhibitor), no statistically significant difference was observed for overall survival (OS) or disease-free survival (DFS). Nonetheless iniparib was subsequently regarded as not a true PARP inhibitor.[23]

In an ongoing phase II study, a single agent PARP inhibitor ABT-888 (veliparib) followed by post-progression therapy of veliparib with carboplatin was tested in patients with *BRCA*-associated metastatic breast cancer.[22] *BRCA1*- and *BRCA2*-mutated patients were enrolled. The response rates to veliparib were 15% and 37%, respectively when veliparib was used alone. When patients crossed over to veliparib with carboplatin at progression, the response rates were 11% and 0%, respectively.[24] Another PARP inhibitor, niraparib, has produced promising results in germline *BRCA*-mutated breast and ovarian cancer patients; in this phase 1 study, 40% of *BRCA1* or *BRCA2* mutation carriers with ovarian cancer (n = 20) achieved a partial response, and 50% of *BRCA* mutation carriers with breast cancer responded (n = 4).[25]

A number of on-going studies are addressing the role of PARP inhibitors in TNBC patients with metastases. The M12-895 study compares the use of carboplatin + paclitaxel versus carboplatin + paclitaxel + veliparib versus temozolomide + veliparib in a randomised setting among *BRCA1*- and *BRCA2*-mutation carriers (NCT01506609). Other ongoing trials of PARP inhibitors in metastatic breast cancer patients with germline *BRCA* mutations include the BRAVO trial that is testing niraparib, the EMBRACA trial (NCT01945775) that is testing BMN673, and the OLYMPIAD study that is using olaparib (NCT02000622). These trials share a similar design in that the single agent PARP inhibitor arm is being compared with physician choice within a standard-of-care options (including capecitabine, vinorelbine, eribulin, or gemcitabine). Progression-free survival is the primary endpoint, and all of these trials have companion diagnostic studies.

NEOADJUVANT SETTING

In a meta-analysis of neoadjuvant clinical trials in breast cancer, the pathological complete remission (pCR) rate according to tumour subtype has been shown to vary; the response rates to neoadjuvant chemotherapy appear to be higher in TNBC and HER-positive tumours than in luminal breast cancers.[26] The pCR rates for luminal A/B, HER2+, and TNBC using T-FAC (paclitaxel, 5-fluorouracil, doxorubicin, and cyclophosphamide) regimen were 7%, 45% and 45% respectively.[27] Using an AC-T (doxorubicin, cyclophosphamide and paclitaxel) regimen, the corresponding figures were 7%, 36%, and 26% respectively; among the patients who achieved pCR, the 5-year distant DFS was over 90%.[3] Although failure to achieve pCR status in luminal A/B breast cancer has not been associated with a poor outcome, failure among TNBC patients with neoadjuvant chemotherapy is associated with a significantly poor prognosis.[3,26]

The role of platinum compounds in TNBC in the context of neoadjuvant chemotherapy was first addressed

in a study by the US Dana-Farber Cancer Institute that involved 28 patients who were treated with four cycles of neoadjuvant chemotherapy using cisplatin; of the six (22%) patients who achieved the pCR, two were identified to be *BRCA1* carriers.[5] The German GeparSixto study randomised 315 TNBC patients to receive paclitaxel + liposomal doxorubicin and bevacizumab with or without carboplatin before surgery (Figure[28]). Of the patients with TNBC, 84 (53%) of 158 patients achieved a pathological complete response with carboplatin, compared with 58 (37%) of 157 without carboplatin (p = 0.005).[28] In the ALLIANCE40603 study conducted by the CALBG, a 2 x 2 factorial design was adopted. Patients received 12-weekly paclitaxel and four cycles of dose-dense doxorubicin + cyclophosphamide, 50% received carboplatin, and 50% received bevacizumab. Among patients who did and did not receive carboplatin, the pCR rate was 60% and 44%, respectively (p = 0.0018). Among patients who did and did not receive bevacizumab, the pCR rates were 59% and 48%, respectively (p = 0.0089).[29] However, although this latter study supports the role of platinum in TNBC, interest in the use of bevacizumab would probably be low based on the lack of improvement in DFS and OS in the BEATRICE study (see below).[30] More recently, in the 2014 San Antonio Breast Cancer Symposium, Sharma et al[31] compared carboplatin/docetaxel combination with standard doxorubicin/cyclophosphamide-docetaxel in the neoadjuvant setting among TNBC patients in a prospectively collected registry; 288 TNBC patients were identified, 49 received carboplatin/docetaxel and 43 received doxorubicin/cyclophosphamide-docetaxel. All of these patients underwent BRCA testing. In the carboplatin/docetaxel cohort, 26% were *BRCA1* or *BRCA2* positive, while in the doxorubicin/cyclophosphamide-docetaxel cohort, 9% were *BRCA1* or *BRCA2* positive. Overall, the pCR rate for patients treated with carboplatin/docetaxel versus doxorubicin/cyclophosphamide-docetaxel groups was 62% versus 42%, respectively (p = 0.036). Among the *BRCA*-positive patients, the pCR rate for patients treated with carboplatin/docetaxel versus doxorubicin/cyclophosphamide-docetaxel groups was 61% versus 36% respectively (p = 0.038).[31]

Of note, although platinum appears to yield a high response rate among *BRCA*-mutated patients, *BRCA1*- and *BRCA2*-mutation carriers also have a higher pCR rate to anthracycline-taxane neoadjuvant regimens. The MD Anderson group has reported a pCR rate of 46% for *BRCA* mutant, which is higher than the 22% pCR rate in non-mutants.[32] It is therefore unclear whether the response to platinum is specific when compared with standard care. Trials such as the 12-258 INFORM multicentre study will attempt to address this issue. This is a prospective randomised phase 2 study that compares four cycles of doxorubicin/cyclophosphamide with four cycles of cisplatin in the neoadjuvant setting, followed

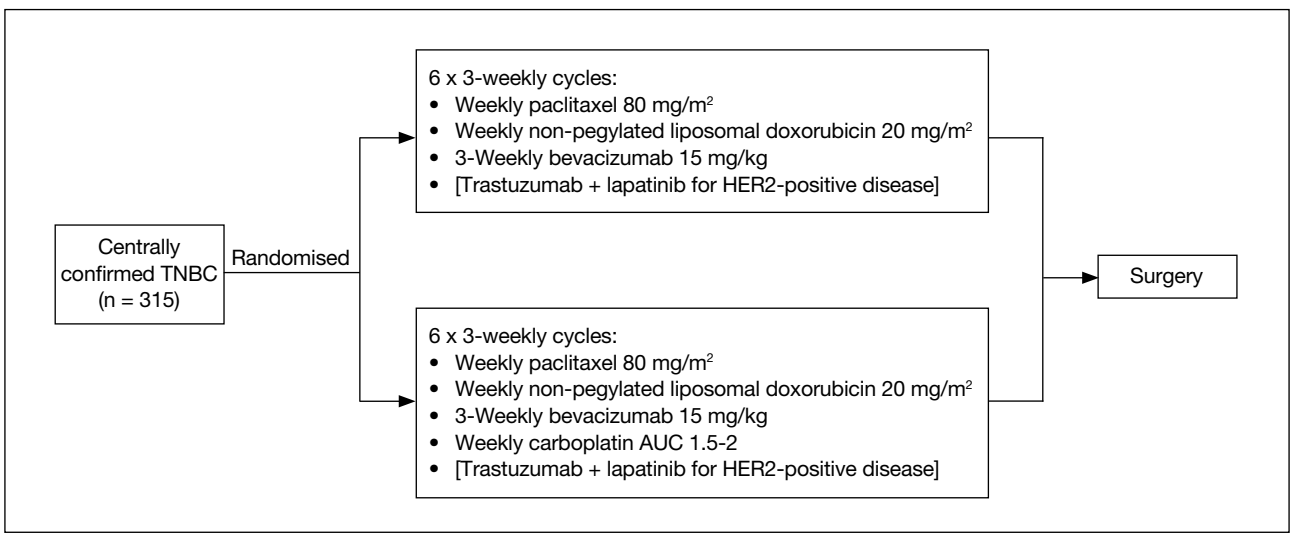

Figure. A schematic illustration of the design of the GeparSixto study.[28]
Abbreviations: AUC = area under the curve; HER2 = human epidermal growth factor receptor 2; TNBC = triple-negative breast cancer.

by additional postoperative chemotherapy in *BRCA1*- and *BRCA2*-mutation carriers (http://core-prognostex.com/trial-support/informbrca-12/).

Although the above data have shown that carboplatin improves pCR rate, the association of pCR with improved survival awaits further confirmation, and as such, a carboplatin-containing neoadjuvant regimen is not yet considered a new standard of care in daily practice. To date, there is no definitive study to show that pCR from neoadjuvant treatment for TNBC has a definitive role in improving DFS or OS. There may be triple-negative subtypes that are particularly sensitive to platinum compounds. The GeparSixto study has reported that increased levels of stromal tumour-infiltrating lymphocytes predict pCR, particularly in patients treated with carboplatin.[33] In addition, von Minckwitz et al[34] reported in a separate study that those patients with germline BRCA or restriction site-associated DNA (RAD) alteration as well as those without germline BRCA or RAD alteration but a family history of breast or ovarian cancers had additional benefit from carboplatin-containing neoadjuvant chemotherapy with increased pCR rate. Of the 315 participants of GeparSixto with TNBC, 295 (94%) had blood samples with sufficient DNA for analysis. A total of 38 mutation carriers (35 *BRCA1*, 3 *BRCA2*) were identified, another 78 patients had a known family breast cancer history, and 179 patients had, to date, neither a mutation nor a family history. The overall pCR rate increased from 40% in patients with no identified risk, to 45% in patients with family history only, and 58% for patients with a germline *BRCA* mutation. Further, the addition of carboplatin to paclitaxel-liposomal doxorubicin combination increased the pCR rate by 14% (odds ratio [OR] = 1.79) in patients without increased risk, by 20% (OR = 2.29) in patients with a family history only, and by 25% (OR = 2.75) for patients with a germline BRCA mutation.[34]

With regard to PARP inhibition in the neoadjuvant setting, the role of PARP inhibitors has been tested in a phase II study reported by Telli et al.[35] In this study, 80 patients with TNBC or *BRCA1/2* mutation were treated with gemcitabine, carboplatin, and iniparib prior to surgery. Those with *BRCA1* or *BRCA2* mutations and those who had TNBC plus *BRCA1* or *BRCA2* mutations had a higher pCR rate. In addition, patients who were not *BRCA1*- or *BRCA2*-mutation carriers, but who had a high HRD score, also responded better to this treatment, suggesting a relationship between a biomarker and disease response.[35] A current study with biomarker correlative analysis is being conducted in the RIO Window Trial that is assessing the role of the PARP inhibitor, rucaparib, in 70 sporadic TNBC and up to 15 *BRCA1* or *BRCA2* mutants.[36]

Systemic Treatment of Residual Disease

Patients who have residual disease following neoadjuvant chemotherapy is another challenging issue. For them, the current standard of care would be no further therapy, but there are a number of clinical trials that are targeting this patient population. The Hoosier Cancer Research Network BRE09-146 is testing the role of cisplatin with or without rucaparib among TNBC or *BRCA* mutation–positive patients who have residual disease following neoadjuvant chemotherapy.[37] Overall, 128 patients who have undergone neoadjuvant chemotherapy and have post-treatment residual disease will be randomised to one of two arms in this study.[37] The primary endpoint is 2-year DFS. In the 2014 American Society of Clinical Oncology meeting, the preliminary 1-year DFS was presented. Overall, there was no difference in 1-year DFS between the two arms. However, for patients with *BRCA* mutations, the 1-year DFS was 84.6% in the cisplatin alone arm versus 100% in the cisplatin plus rucaparib arm.[37]

There are other ongoing studies addressing the role of additional therapy for residual disease following neoadjuvant chemotherapy in TNBC. The ECOG/ACRIN trial will enrol patients who have residual disease following anthracycline- and taxane-containing neoadjuvant chemotherapy to determine whether the addition of platinum improves outcome when compared with standard care of no further therapy. The Olympia study focuses on the BRCA + TNBC patients; those who have residual disease following neoadjuvant chemotherapy and those with large tumour size (T2) or node-positive disease who are scheduled for postoperative adjuvant chemotherapy will be randomised to 12 months of olaparib or placebo; the study endpoints are DFS and OS. With tissue-based research, the TBCRC030 study will determine whether a response to chemotherapy (either with cisplatin or weekly paclitaxel) among *BCRA* carriers can be predicted using HRD as a potential biomarker.[38]

ADJUVANT SETTING IN TRIPLE-NEGATIVE BREAST CANCER

The Oxford Overview analysis has shown that patients with ER-negative disease (among whom about two-

thirds are estimated to be TNBC) benefited from four or more cycles of anthracycline-containing adjuvant chemotherapy; this was associated with a reduction of disease recurrence by 7%.[39] In the CALBG study that compared the difference in benefits from adjuvant chemotherapy achieved by patients with ER-negative versus ER-positive node-positive tumours,[40] the improvement in breast cancer outcome was seen disproportionately in ER-negative breast cancers; among ER-negative cancers, adjuvant chemotherapy reduced the risk of breast cancer recurrence and death by 63% and 59% respectively, while within the ER+ disease, the corresponding risk reduction was 32% and 8% respectively. With earlier regimens such as CMF (cyclophosphamide, methotrexate, and fluorouracil), the IBCSG has shown in a retrospective study that the regimen was notably effective in the subgroup of patients with TNBC.[41] With the improvement in adjuvant cytotoxic treatment, improved outcomes have been demonstrated, particularly in ER-negative disease, and to a large extent in TNBC. The CALBG 9344 was one of the first studies to test the role of paclitaxel in the adjuvant setting; subgroup analysis revealed that the use of taxane in addition to anthracycline-cyclophosphamide chemotherapy improved DFS in patients with ER-negative HER2-negative as well as ER-negative HER2-positive disease.[42]

With respect to the role of biological agents in TNBC, the BEATRICE study was a randomised phase 3 trial that recruited patients with centrally confirmed early TNBC; patients were allocated to receive a minimum of four cycles of adjuvant chemotherapy either alone (1290 patients) or with 1 year of bevacizumab (1301 patients). At a median follow-up of 32 months, invasive disease-free survival (IDFS) events had been reported in 205 (16%) patients in the chemotherapy-alone group and in 188 (14%) patients in the bevacizumab group ($p = 0.18$). The 3-year IDFS was 82.7% with chemotherapy alone and 83.7% with bevacizumab and chemotherapy. After 200 deaths, no difference in OS was noted between the groups (hazard ratio = 0.84; 95% confidence interval, 0.64-1.12; $p = 0.23$). Thus, to date, there has been no effective biological agent in the treatment of early TNBC.[30]

Despite the fact that biology plays a vital role in the prognosis of breast cancer patients, stage remains an important prognosticator. For early-stage disease, the outcome of patients with TNBC remains very good. For instance, the MD Anderson data reported that patients with T1a-b N0 TNBC who did not receive adjuvant chemotherapy have a 5-year distant relapse-free survival (DRFS) of 96%.[43] In a larger dataset reported from the NCCN, 4113 women with T1a-bN0M0 breast cancer who were treated between 2000 and 2009 were included. Among these patients, those with hormone receptor-negative/HER2-negative T1a tumours and T1b tumours who did not receive chemotherapy had a 5-year DRFS of 93% (n = 74) and 90% (n = 94) respectively, and the 5-year DRFS for treated patients was 100% (n= 25) and 96% (n= 170) respectively.[44] Based on these data, the NCCN guideline has recommended that similar to patients with pT1cN0 and above disease, patients who have pT1bN0 disease should be considered for adjuvant chemotherapy.[45] Similar to patients with other tumour subtypes, although regimens including anthracycline-containing, taxane-containing, as well as anthracycline- and taxane-containing regimens (including dose-dense regimen) can be considered for TNBC patients, the concurrent use of anthracycline and taxane is generally considered to be more toxic when compared with sequential treatments. The St Gallen International Expert Consensus on the Primary Therapy of Early Breast Cancer 2015 will provide more insight into the management of this patient subgroup.

CONCLUSION

TNBC is a distinct breast cancer subtype in which further distinct sub-classifications exist. TNBC represents an important clinical challenge in which the present mainstay of systemic treatment remains to be chemotherapy only. Research into potential therapeutic strategies specifically to address TNBC is required. A number of potential targets are currently under investigation and may improve the outcome for patients with TNBC.

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