

PARP inhibitor and platinum agent in triple negative breast cancer: utilizing innovative trial design to bring together something “new” and something “old”

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Introduction

Triple negative breast cancer (TNBC) which is defined by the lack of expression of estrogen receptor (ER) and progesterone receptor (PgR), and absence of human epidermal growth factor receptor 2 (HER2) over expression and/or gene amplification accounts for approximately 15–20% of all breast cancers. TNBC is currently the most lethal subtype of breast cancer and is associated with poor long-term outcomes compared to other breast cancer subtypes (1,2). Compared to other breast cancer subtypes TNBC usually demonstrates high pathologic grade, more frequently affects younger women, is more prevalent in African American women and shows a higher prevalence of germline *BRCA* mutation (3-5). Over the last two decades institution and/or enhancement of targeted therapies has improved the outcomes of HER2 amplified and hormone positive breast cancers. However, these recent advances in targeted therapies have evaded TNBC due its tremendous heterogeneity and the lack defined molecular targets. Despite receiving standard anthracycline-taxane based chemotherapy, a significant proportion (30–40%) of patients with early stage TNBC develop metastatic disease and succumb to the cancer (6,7). Compared to hormone positive breast cancer TNBC is characterized by a higher proportion of visceral relapse and very short survival after development of metastatic disease (8,9). Median survival

of patients with metastatic TNBC is only 12–18 months compared to 5 years for patients with metastatic HER2 positive breast cancer, highlighting the pressing need for identification of more effective systemic therapies for this subgroup.

Sporadic and germline *BRCA* mutation associated TNBC share several pathological and molecular similarities. These similarities have led to the exploration of DNA damaging agents like platinum compounds in the general population of patients with TNBC. Growing evidence suggests that platinum compounds may be active in a significantly larger number of TNBC patients beyond germline *BRCA* mutation carriers (10,11). Currently, anthracyclines (A), cyclophosphamide (C) and taxanes (T) form the backbone of systemic chemotherapy for stage I–III TNBC. Recent studies demonstrate that addition of neoadjuvant carboplatin (Cb) to A and T based chemotherapy improves pathological complete response (pCR) in patients with stage I–III TNBC (12,13). However, the long-term outcomes from the addition of platinum in a neoadjuvant setting for TNBC are not yet clear.

Poly (ADP-ribose) polymerase (PARP) enzymes recognize DNA damage and facilitate DNA repair to maintain genomic stability. Preclinical studies demonstrate that PARP inhibition in the presence of *BRCA* deficiency leads to synthetic lethality. PARP inhibitors (PARPi) have

shown preclinical and clinical activity in targeting tumors with pre-existing DNA repair defects, in particular BRCA1 and BRCA2-deficient advanced breast and ovarian tumors (14–18). As a significant proportion of TNBCs are thought to harbor DNA repair defects, it might be possible to extend the observation of PARPi sensitivity of germline BRCA-associated tumors to BRCA wild-type TNBCs that harbor BRCAness phenotype. Accordingly, PARPi are being explored in the general population of patients with TNBC.

Clinically, neoadjuvant chemotherapy has a number of potential advantages especially for TNBC. Decreasing the size of the primary tumor may make breast conservation more likely, and can also lead to eradication of occult axillary nodal disease. Additionally, it allows for immediate objective assessment of chemotherapy response which offers prognostic information, as well as can potentially guide alterations in therapy. Finally and most importantly, neoadjuvant chemotherapy allows for rapid preliminary assessment of new treatment approaches and to study the relationship between biologic markers and treatment response. The Investigation of Serial Studies to Predict Your Therapeutic Response through Imaging and Molecular Analysis 2 (ISPY-2) trial demonstrates in exemplary fashion how this aspect of neoadjuvant treatment can be leveraged for advancement of breast cancer therapy.

I-SPY 2 veliparib-Cb results

I-SPY 2, is a phase 2, multicenter, adaptively randomized trial to screen multiple experimental agents/regimens in combination with standard AC/T based neoadjuvant chemotherapy for breast cancer. The goals of this study are to match experimental regimens with responding cancer subtypes. Patients with stage II or III breast cancer are enrolled and categorized into eight biomarker subtypes on the basis of HER2 status, hormone receptors status, and a 70-gene assay status. Patients undergo adaptive randomization within each biomarker subtype to receive regimens that have better performance than the standard therapy. Regimens move on from phase 2 if and when they have a high Bayesian predictive probability of success in a subsequent phase 3 neoadjuvant trial within the biomarker signature in which they performed well.

In a recent article Rugo *et al.* reported results for veliparib, (PARPi), combined with Cb when added on to standard therapy in HER2-negative breast cancer (19). A total of 72 patients (triple negative =39, hormone positive =33) were randomly assigned to receive veliparib (50 mg PO

BID ×12 weeks) + Cb (AUC 6 every 21 days ×4) + paclitaxel (weekly ×12) followed by AC ×4 cycles, and 44 patients (triple negative =21, hormone positive =23) were concurrently assigned to receive standard therapy (weekly paclitaxel ×12 followed by AC ×4). In TNBC patients, the veliparib-Cb regimen yielded an estimated pCR rate of 51% [95% Bayesian probability interval (PI), 36% to 66%], as compared with 26% (95% PI, 9% to 43%) for standard therapy, which suggested that a confirmatory randomized trial of 300 patients involving this regimen in TNBC would have a 88% predicted probability of success. The benefit of veliparib-Cb was restricted to TNBC as the estimated rate of pCR among patients with hormone-receptor-positive (and HER2-negative) breast cancer was 14% (95% PI, 3% to 25%) in the veliparib-Cb group and 19% (95% PI, 5% to 33%) in the control group.

The toxicity of veliparib-Cb was greater than that of the control. The rate of grade 3 or 4 hematologic toxic effects was higher in the veliparib-Cb group than in the control group (71% *vs.* 2% of patients had neutropenia, 1% *vs.* 0% had febrile neutropenia, 21% *vs.* 0% had thrombocytopenia, and 28% *vs.* 0% had anemia). Dose reductions of Cb occurred in 47% patients. Dose reductions of paclitaxel occurred in 32% patients in the veliparib-Cb group and in no patients in the control group. Eighteen percent of patients in the veliparib-Cb group, as compared with 5% in the control group discontinued therapy early. The authors also note a higher median time from treatment consent to surgery in experimental arm compared to control (182 *vs.* 165 days) presumably due to treatment delays related to toxicity. There was also some imbalance in the proportion of patients with germline *BRCA1/2* mutations in the two arms as more patients in the veliparib-Cb group than in the control group carried a deleterious *BRCA1/2* mutation (17% *vs.* 7%). pCR rates in relationship to *BRCA* mutation status was not reported in the publication.

The ISPY-2 trial is an important trial that uses a novel trial design approach. Rather than using a fixed framework of statistical assumptions to determine sample size and power, the trials reacts to results as they arrive. This adaptive approach potentially allows for faster and more flexible trial design. Based on this report by Rugo *et al.* the combination of veliparib-Cb has graduated for evaluation in a phase III trial.

An ongoing phase 3 neoadjuvant trial is comparing the efficacy of standard chemotherapy alone, with Cb, or with veliparib plus Cb as neoadjuvant treatment for triple-negative breast cancer (ClinicalTrials.gov number,

NCT02032277). This trial has recently completed accrual and results are eagerly awaited.

In context with other neoadjuvant platinum studies

Recent studies have focused on role of platinum agents when used as component of neoadjuvant therapy in TNBC. Three randomized studies have demonstrated that addition of neoadjuvant Cb to anthracycline/taxane based chemotherapy improves pCR in patients with stage I–III TNBC (pCR improvement from approximately 41% to 54% with addition of Cb) (12,13,20). Other investigators have also reported encouraging pCR rates ranging from 36–65% with anthracycline-free taxane-platinum regimens in TNBC (21).

Since the investigational regimen in the ISPY-2 study included addition of both a PARPi and a platinum drug, it is possible that the improvement in pCR was driven partially or entirely by the platinum drug rather than by the combination of platinum plus PARPi. As stated by the ISPY-2 authors the trial was not designed to evaluate the individual contributions of veliparib and Cb. This question will be answered by the recently completed larger Neoadjuvant study (NCT02032277).

The five drug neoadjuvant ISPY-2 regimen did demonstrate modest toxicities. Increase in hematological toxicity and dose reduction of standard chemotherapy drugs have been noted with addition of Cb to A/T chemotherapy backbone in other studies. It is evident from previous studies that 35–40% of TNBC patients will have a complete pathological response with the conventional AC-T chemotherapy thus addition of platinum ± PARPi to standard chemotherapy for unselected TNBC raises concerns regarding substantial overtreatment of a large proportion of the patient population. Thus, developments of response biomarkers are critical for safe and effective incorporation of these agents in clinical practice.

Looking ahead

Several studies are also looking at combination of PARPi and platinum based DNA damaging chemotherapy in TNBC. Brightness study (NCT02032277) will assess the activity of veliparib in combination with Cb in neoadjuvant setting in both BRCA-associated and wild type TNBC. SWOG 1416 will use a combination of PARPi and cisplatin to test for PARPi activity in both BRCA-associated and

BRCAness phenotype metastatic TNBC.

Given the molecular heterogeneity of TNBC, it is very likely that platinum agents and PARPi will benefit only a subgroup of patients with TNBC. Ongoing and future translational studies should focus on identifying TNBC patients most likely to benefit from such approaches. The authors of ISPY-2 noted that DNA-repair deficiencies were evaluated in all patients but the results are not reported yet.

PARPi are not available for commercial use in breast cancer however platinum agents are available. While we await the completion and outcomes from the randomized studies, oncologists continue to be faced with decisions regarding utility of platinum agents for TNBC in day-to-day practice. The ideal approach for patients and physicians is to seek participation in one of the many ongoing neoadjuvant trials. In an event when a suitable trial is not available, the decision for incorporation of platinum in neoadjuvant treatment of a patient with TNBC should be individualized. Even though long-term outcome data is not clear, the individual patient benefit from attainment of pCR may still justify use of neoadjuvant platinum in select patients.

In conclusion the ISPY-2 investigators should be congratulated on using innovative trial design for identifying agents appropriate for further evaluation in larger phase III studies. Efforts like these are bound to produce progress in treatment of breast cancer.

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None.

Footnote

Conflicts of Interest: The author has no conflicts of interest to declare.

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