Breast Cancer RESEARCH

EDITORIAL

Platinum chemotherapy for *BRCA1*-related breast cancer: do we need more evidence?

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Abstract

A recent prospective clinical trial provides further evidence that breast cancers arising in germline *BRCA1* mutation carriers are highly sensitive to cisplatin chemotherapy. The potential significance of these data for the management of patients with *BRCA1*-related and *BRCA2*-related breast cancer is discussed.

In a previous issue of *Breast Cancer Research* Tomasz Byrski and colleagues present the results of a prospective phase II study of cisplatin in *BRCA1*-related metastatic breast cancer – that is, breast cancer arising in women with a germline mutation in *BRCA1* [1]. They report evidence of substantial efficacy with an overall response rate of 80%, including 45% with complete response, and a time to progression of 12 months. The majority of patients in the study had triple receptor-negative breast cancer, and this time to progression compares favorably with median progression-free survival for triple receptor-negative breast cancer in contemporary series [2]. This study follows on from a retrospective study by the same group that reported a pathological complete response rate of 83% with neoadjuvant cisplatin chemotherapy, compared with a rate of 15% with nonrandomized comparator neoadjuvant chemotherapy [3].

The molecular basis for these high response rates is well understood. Both BRCA1 and BRCA2 are required for DNA double-strand break repair by homologous recombination (HR-based DNA repair) [4,5]. Mutations in *BRCA1* and *BRCA2* inactivate protein function, and in cancer the wild-type allele is almost invariably lost, leading to a defect in HR-based DNA repair in the cancer. Platinum chemotherapy generates interstrand cross-links that can only be adequately repaired by HR-based DNA repair, and consequently *BRCA1*-deficient and *BRCA2*-deficient cells are highly sensitive to platinum chemotherapy both *in vitro* and *in vivo*. With high response rates in a prospective clinical trial, and a strong biological rationale, it is time to ask whether we are moving towards a new chemotherapy standard for *BRCA1*-related, and potentially by inference *BRCA2*-related, breast cancer or whether we need more evidence.

The main strength of the current study is that it has been carried out at all. *BRCA1* mutations account for a small proportion of patients with advanced breast cancer, even in countries with founder mutations, and this presents a substantial barrier to running studies testing standard chemotherapy. Use of the chemotherapy regimen outside the trial, and the wide availability of novel therapy trials competing for the same patients, add to the challenges of recruiting such trials. Nevertheless, the study by Byrski and colleagues is an open-label single-arm study of only 20 patients, with no central radiological confirmation of response rates, and both this study design and this size make a meaningful interpretation of progression-free survival very difficult. The study was in addition not prospectively registered in a clinical trial registry, removing one of the safeguards against publication bias.

The study is dominated by women with three specific mutations in *BRCA1* that represent the three founder mutations found in the Polish population [1], with over one-half being the single mutation 5382insC. One of these mutations, C61G, is predicted not to sensitize to cisplatin on the basis of preclinical data [6] yet cancers with this mutation appear to be just as sensitive to cisplatin in the study [1], a discrepancy for which it is important to understand the basis. Prior studies reported by this group have also been drawn from the Polish founder mutations, and we have limited data on the response of cancers with other *BRCA1* mutations, and very limited data for *BRCA2* mutations.

Although the data for *BRCA1/2*-related breast are therefore relatively limited, there are substantial data on the sensitivity of *BRCA1*-related and *BRCA2*-related

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ovarian cancers to platinum-based chemotherapy [7,8]. *BRCA1/2*-related serous ovarian cancers are highly sensitive to platinum chemotherapy, and remain sensitive to repeat challenges with platinum chemotherapy, which likely explains the improved survival of *BRCA1/2*-related serous ovarian cancer compared with *BRCA1/2* wild-type serous ovarian cancer [8].

Should the accumulation of data, which includes this study by Byrski and colleagues, alter our approach to the treatment of *BRCA1*-related and *BRCA2*-related breast cancer? For patients with metastatic *BRCA1*-related breast cancer, although the data are limited, it seems clear that these patients should be offered the option of platinum-containing chemotherapy at some point during their treatment course. Whether platinum chemotherapy should be used as the first line in preference to other chemotherapy agents is unclear, and this is the subject of the BRCA trial (NCT00321633, NCT00532727) that randomizes first-line patients between carboplatin and docetaxel. For those with *BRCA1* mutation-associated triple receptor-negative breast cancer and anthracycline-resistant and taxane-resistant disease, where there are few available active therapies, and the option of platinum-agent chemotherapy seems well founded.

Whether the platinum agent should be cisplatin or whether carboplatin would have a similar response rate is unknown. Any difference in efficacy between the two drugs is likely to be small and may be outweighed by logistical and toxicity advantages for the patient. Whether patients with evidence of disease response and a long platinum-free interval (>6 months off chemotherapy) should be retreated with platinum-based chemotherapy on progression or whether they should be treated with alternative chemotherapy regimens remains unclear, and we await data to guide such decisions. Although there are few direct data on *BRCA2*-related breast cancer, the strength of the biological rational, the comparative data between *BRCA1* and *BRCA2* in ovarian cancer, and the evidence of poly(ADP ribose) polymerase (PARP) inhibitor efficacy in *BRCA2*-related breast cancer [9] all suggest that similar advice should apply to *BRCA2*-related breast cancer.

What about the curative setting and patients receiving adjuvant or neoadjuvant chemotherapy? Here the data are less robust. Standard adjuvant anthracycline/taxane chemotherapy cures a substantial proportion of women with breast cancer, with evidence of better outcomes and therapy responses in the *BRCA1/2* carrier population [10,11], so changes to this standard should only be made on the basis of strong evidence. At present the data to support platinum agents in this context are limited to retrospective analysis [3] or to prospective data for a very small number of patients [12]. Prospective studies are still required before routine practice changes in the curative setting. The one current exception to this is in the treatment of *HER2*-positive breast cancer in *BRCA1/2* carriers. Relative equipoise has already been shown in the general breast cancer population for the TCH (docetaxel, carboplatin, trastuzumab) regimen compared with standard anthracycline–taxane–trastuzumab-based chemotherapy [13], and the TCH (docetaxel, carboplatin, trastuzumab) regimen presents an attractive option for *BRCA1/2* carriers with *HER2*-positive breast cancer.

PARP inhibitors target the same HR-based DNA repair defect as cisplatin chemotherapy, and there is evidence of efficacy for the PARP inhibitor olaparib in *BRCA1*-related and *BRCA2*-related breast cancer with substantial prior chemotherapy exposure [9]. PARP inhibitors target the DNA repair defect in a more specific fashion and are well tolerated without typical chemotherapy side effects [9]. The challenge in *BRCA1/2*-related advanced breast cancer is to develop and support a collaborative mechanism where patients can be identified and entered into randomized trials that test novel therapies such as PARP inhibitors, or mechanistically based chemotherapy, to robustly assess the efficacy relative to standard care, and therefore allow these patients to benefit from these *BRCA1/2*-focused treatments.

Abbreviations

HR, homologous recombination; PARP, poly(ADP ribose) polymerase.

Competing interests

The authors declare that they have no competing interests.

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