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Editorial

Synthetic lethality and the emerging role of BRCA1/2 as a predictive marker for HER2 negative metastatic breast cancer: analysis of the phase III OlympiAD trial

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Abstract

In the pivotal phase III trial, olaparib demonstrated improved progression-free survival and superior health-related quality of life compared to standard chemotherapy in patients with HER2-negative metastatic breast cancer with germline *BRCA1/2* mutation. Future studies that investigate the use of olaparib in combination with other cytotoxic agents to further induce synthetic lethality are warranted.

Keywords: Olaparib; BRCA1/2; Breast Cancer

Introduction

Breast cancer is the second leading cause of cancer death in American women. In 2016 alone, there were an estimated 249,260 newly diagnosed cases of breast cancer with expected mortality totaling 40,890 [1]. In the unselected breast cancer population, approximately 5% carry a deleterious germline *BRCA1/2* mutation, which is associated with an increased risk for bilateral breast cancer and ovarian cancer [2,3]. However, its significance in the metastatic setting is still unknown [4]. In fact, current utilization of the *BRCA1/2* mutation is solely a prognostic marker and does not dictate a difference in treatment modalities [5].

In the recent years, however, the development of poly(adenosine diphosphate-ribose) polymerase (PARP) inhibitors have shown single-agent activity against BRCA1/2-mutated tumors in the metastatic setting [6,7,8]. PARP inhibitors induce synthetic lethality in BRCA1/2-mutated cells by blocking PARP's role in base excision repair of DNA single-strand breaks (SSBs). At the replication fork, these SSBs may lead to double-strand breaks, which are normally resolved by BRCA1 and BRCA2 [9]. However, in BRCA1/2-mutated cells, these resolutions cannot occur and thus, the accumulation of DNA damage leads to cell death [10]. Olaparib, a PARP inhibitor, has demonstrated improved progression-free survival (PFS) in BRCA1/2-mutated high grade ovarian cancer patients [11]. In metastatic castration-resistant prostate cancer, BRCA1/2-mutated patients also achieved higher responses to olaparib compared to those without BRCA2 mutations [8]. Based on the prognostic role of BRCA1/2, olaparib may exhibit a desirable role in BRCA1/2-mutated metastatic breast cancer patients as well.

In their recent publication in the New England Journal of Medicine, Robson et al examined the use of olaparib in BRCA1/2 metastatic breast cancer patients in the associated phase III study, the OlympiAD trial. The trial evaluated the use of olaparib monotherapy versus single-agent chemotherapy of physician's choice (capecitabine, eribulin, or vinorelbine in 21-day cycles) in patients with human epidermal growth factor type 2 (HER-2) negative metastatic reast cancer with a germline BRCA1/2 mutation [12]. In both arms, roughly 50% of patients had hormone-receptor positive and 50% had triple-negative disease. Patients with hormone-receptor positive disease were required to have received and progressed on at least one endocrine therapy. 71% of enrolled patients had received prior chemotherapy for metastatic disease and 26% of patients had received platinum-containing chemotherapy in the neoadjuvant, adjuvant, or metastatic setting.

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The primary endpoint of PFS, defined as time from randomization to objective progression based on the modified RECIST criteria version 1.1, was 7.0 months and 4.2 months for olaparib- and standard therapy-treated groups. The response rate was 59.9% and 28.8% for the olaparib- and standard therapy- treated groups. Because of the decrease in disease progression, the investigators noted a 42% relative risk reduction of death with olaparib monotherapy compared to standard therapy. However, overall survival (OS) was similar between both groups. Median time to death was 19.3 months and 19.6 months for olaparib- and standard therapy- treated groups. The investigators noted that the study was not adequately powered to assess these differences and that furthermore, OS in the standard therapy group was confounded by a higher number of these patients transitioning to PARP inhibitors, platinum-based therapy, and cytotoxic chemotherapy for subsequent therapy.

Olaparib demonstrated superior health-related quality of life and safety compared to standard therapy. The time to a clinically meaningful decrease in quality of life, based on QLQ-30 score, was not reached in the olaparib group and 15.3 months for standard therapy. Grade 3 or higher adverse events were seen in 36.6% and 50.5% of olaparib- and standard therapy-treated patients, and adverse events of any grade leading to treatment discontinuation were seen in 4.9% and 7.7% of olaparib- and standard therapy- treated patients. Of note, however, grade 3 or higher anemia events were four times higher in olaparib patients compared to standard therapy at 16.1% vs. 4.4%. The number of blood transfusions required due to grade 3 or higher anemia was not included in the study.

Because there is currently no cure for stage IV or recurrent metastatic breast cancer, principles that govern treatment focus on prolonging survival and enhancing the quality of life [13]. For patients with HER-2 negative and endocrine-refractory metastatic breast cancer, the preferred single chemotherapy agents are anthracyclines, taxanes, anti-metabolites, or other microtubule inhibitors [14]. However, cytotoxic chemotherapy may lead to a lower quality of life, as seen in the adverse events in the OlympiAD trial, which is especially important in the palliative setting.

Improvement in PFS and not OS also opens the discussion of whether targeting one specific driver mutation in the metastatic setting is sufficient [15]. Perhaps a multi-mechanistic approach is warranted to further potentiate antitumor activities. One promising future direction is the use of platinum-based agents in combination with olaparib to induce synthetic lethality. In a phase I trial, cisplatin 75 mg/m^2 and olaparib 50-200 mg BID showed a 71% objective response rate in BRCA1/2 breast cancer patients, compared to 41% in the overall treated patients with measurable disease. However, the combination caused intolerable side effects, in which 55.6% of patients required colony-stimulating factors for hematologic support with subsequent dose de-escalation to cisplatin 60 mg/m^2 and olaparib 50 mg BID [16]. On the other hand, carboplatin may increase the cytotoxic effects of olaparib without undue toxic effects. In one phase I/Ib study, administering carboplatin dosed with an AUC 3-5 prior to olaparib 100-200 mg BID increased the intracellular concentration of olaparib and decreased bioavailability [17,18]. A phase I REVIVAL trial and phase II PARTNER trial are currently underway that investigate the additive role of olaparib in platinum-based chemotherapy in *BRCA1/2*-mutated HER2-negative breast cancer patients [19,20].

The OlympiAD trial is an important milestone in our understanding of BRCA1/2 as a predictive marker for HER2-negative metastatic breast cancer patients with germline BRCA1/2 mutation. Clinical trials that investigate the use of olaparib in combination with other cytotoxic agents to further induce synthetic lethality are warranted.

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