CURRENT ONCOLOGY COMMENTARY

Have we given up on a cure for ovarian cancer?

A Countercurrents Series[a] with S.A. Narod MD*

In December 2014, on the FORCE Web site, executive director Sue Friedman, heralded a game-changing holiday gift for people with *BRCA* mutations: "Today is a landmark for the HBOC [hereditary breast and ovarian cancer] community" [1]. In an accompanying article [2], Lisa Rezende wrote about the U.S. Food and Drug Administration (FDA) decision to approve olaparib for the treatment of recurrent ovarian cancer in women with a *BRCA1* or *BRCA2* mutation:

> The FDA has approved Lynparza [AstraZeneca, Wilmington, DE, U.S.A.] (also known as olaparib) to treat ovarian, fallopian tube, and primary peritoneal cancer in women who carry mutations in *BRCA1* or *BRCA2*, and who have received three or more chemotherapy treatments. Lynparza is the first PARP [poly ADP ribose polymerase] inhibitor to be approved, and the first drug that requires patients to undergo testing for a *BRCA* mutation before they can receive it.
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> While the approval of Lynparza is a great first step in treating cancers in *BRCA* mutation carriers, much work remains. Lynparza has been approved for use in ovarian cancer patients who received three prior chemotherapies, making it what is known as a "fourth line" drug. More research is still needed to determine if PARP inhibitors will work in other settings. Ongoing clinical trials are enrolling patients with cancer to answer these questions.

"Much work remains" is an understatement—akin to saying that recurrent ovarian cancer is "difficult to treat." Notable in Rezende's words, and in statements elsewhere in the press, is that that no one says exactly how good olaparib actually is. What does Rezende mean when she says that a PARP inhibitor "works"—in the fourth-line ovarian cancer setting or in any other setting?

Olaparib is approved only for women with recurrent cancers who have received three or more lines of chemotherapy: that is, for those unfortunate women who are already destined to die of their cancer. In no study that I have seen does olaparib prevent women from dying of cancer or even delay their death. It has been associated with improvements in progression-free survival: that is, when given either alone [3] or in combination with cisplatin or carboplatin [4] to women who responded to platinum, olaparib delayed cancer recurrence.

In the first study [3], in women with a *BRCA* mutation and platinum-sensitive recurrent ovarian cancer, olaparib prolonged the time to recurrence to 11.2 months from 4.3 months, but the median time to death was a stolid 34.9 months in the olaparib group compared with 31.9 months in the control group ($p = 0.19$). In the second study [4], in an overall patient population, time to progression was 12.2 months in the chemotherapy plus olaparib group and 9.6 months in the chemotherapy-alone group. The difference was greater in the *BRCA*-positive subgroup, but that group was small (41 patients), and compared with women who did not take olaparib, mutation-positive women who took olaparib did not experience an extended time to death (hazard ratio: 1.28; 95% confidence interval: 0.39 to 4.18; $p = 0.69$). Those important details are glossed over on the FORCE Web site, which bills itself as an information resource for women with ovarian cancer.

We are in an optimistic season, but reality is sobering. Since 1977, no increase has been achieved in the percentage of women who survive ovarian cancer. For practical purposes, cure of ovarian cancer is well approximated by 12-year survival: In an Ontario study, only 1 of 309 patients with ovarian cancer who survived for 12 years ultimately died of the disease [5], meaning that no rise in the cure rate has been evident despite the improvements in 5-year survival, life expectancy, and median survival that accompanied the introduction of platinums and taxanes. Ovarian cancer is unusual because survival curves that separate at 5 years invariably come together at 10 years—regardless of the drug used.

It is a convenient property of non-proportional hazard curves that they afford statisticians the opportunity to represent survival in almost any way they like. Progression is not a surrogate for overall survival [6]. I can understand why drug companies would choose metrics that present their product in the most favourable light. I also understand why a physician would want to relay prognosis in a way that gives a patient hope, but I think that medical oncologists should adhere to a standard that is both high and consistent with evidenced-based medicine.

The cost of olaparib is estimated to be $3000 per month. In one risk analysis [7], the cost of olaparib to extend progression-free life by 1 year was $234,128 (the investigators failed to factor in the fact that olaparib shortened survival time from progression to death by an equal amount). AstraZeneca is predicting $2 billion in annual sales for Lynparza, which arose from discoveries made by

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Professor Steve Jackson's Cancer Research UK–funded team in Cambridge, and which has just been recommended for January approval by the European Medicines Agency: "Cambridge is getting closer to giving the world a second blockbuster drug" [8]. It is good that academia should partner with industry in the development of cancer drugs, but is it not a conflict of interest that the Cancer Research UK–funded research team should be a vocal partner in the marketing of a drug by supporting disingenuous claims about its effectiveness? Does the term "blockbuster" refer to the expected revenue or the expected number of lives saved?

In another development, Myriad Genetics of Salt Lake City, Utah, announced that it had received approval from the FDA for BRAC*Analysis* CDX to be used as the only companion diagnostic in conjunction with AstraZeneca's Lynparza [9]:

> BRAC*Analysis* CDX is Myriad's first FDA-approved companion diagnostic for use with a novel PARP inhibitor.
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> "Myriad is excited to offer the first and only FDA-approved companion diagnostic for Lynparza, which we believe opens a new door in personalized medicine and represents a big step forward in tailoring treatment for women with ovarian cancer," said Mark Capone, president, Myriad Genetic Laboratories. "Less than 25 percent of ovarian cancer patients know their germline *BRCA* status, which is critical for any ovarian cancer patient who may be considered for treatment with Lynparza."
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> BRAC*Analysis* CDX is a highly accurate molecular companion diagnostic test that identifies deleterious or suspected deleterious mutations in the *BRCA1* and *BRCA2* genes, using DNA obtained from a blood sample. BRAC*Analysis* CDX was proven in clinical studies to effectively identify patients with *BRCA* mutations who would be candidates for Lynparza. The approval of BRAC*Analysis* CDX demonstrates Myriad's commitment to developing companion diagnostics and is the culmination of an intensive, multiyear scientific collaboration with AstraZeneca to advance personalized medicine for women with ovarian cancer.

Until now, I had no idea that it was necessary to obtain FDA approval to perform a straightforward genetic test that is being done without fanfare in dozens of genetics laboratories worldwide. How is it that the information from other laboratories is good enough to be used to decide on the use of other drugs, such as platinum agents—or to decide whether a woman should remove her breasts—but is not good enough to support a decision to give olaparib? At the 2014 San Antonio Breast Cancer Symposium, Dr. Andrew Tutt presented data (which extend our group's previous report from Poland [10]) showing that carboplatin is a better drug than doxorubicin for the treatment of metastatic breast cancer in *BRCA* carriers [11]. Will Myriad claim that carboplatin can be given only if the genetic test is BRAC *Analysis* CDX? The term "companion diagnostic" has a friendlier ring to it than "accessory diagnostic" does.

The second drug touted for the treatment of ovarian cancer, and one that is also the subject of a widespread lobbying effort, is bevacizumab. The cost for 9-cycle treatment is approximately $35,000, and the drug should ideally be given monthly in women with recurrent ovarian cancer until they progress. Bevacizumab doesn't cure patients, or even extend their lifespan. The benefit of bevacizumab—like that of olaparib—is restricted to progression-free survival [12,13]. In one study [12], the average time from treatment to progression was 14.1 months for women receiving bevacizumab and 10.3 months for women not receiving it. The average time from treatment to death was 39.7 months for women receiving bevacizumab and 39.3 months for women not receiving it.

"Maintenance therapy" is a term that has been adopted by the medical oncology community to describe the ongoing use of chemotherapy with the goal of lowering the risk of recurrence after initial therapy. The term is borrowed from chronic disease medicine—for example, the use in hypertension and diabetes of drugs that are to be taken by patients indefinitely. The paradigm is that, by virtue of those drugs, medical conditions are transformed from acute into chronic diseases. In some instances—for example, diabetes and AIDS—the results have been spectacular, and the term "maintenance therapy" is justified. However, I do not think it appropriate to suggest that ovarian cancer has been turned into a "chronic disease" by a drug that does not extend survival. To adapt the paradigm of "maintenance therapy" to the case of ovarian cancer, it was necessary first to replace the endpoint of overall survival with that of progression-free survival.

There is no doubt that increasing progression-free survival is worthwhile, but it is not the ultimate goal. Before the introduction of chemotherapy, the hope was for a cure. In his 1971 State of the Union address, U.S. president Richard M. Nixon promised Americans that he would begin "an intensive campaign to find a cure for cancer" [14]. Cisplatin and taxanes are important advances in the treatment of ovarian cancer; however, given the fact that neither drug boosts cure rates, oncologists have switched to describing benefits in terms of hazard ratios, p values, median survival, and life expectancy. With the advent of olaparib and bevacizumab, even those metrics are no longer applicable and—in the name of progress—oncologists again widened the area between the goalposts to accommodate progression-free survival [13].

It is unfortunate that women with recurrent ovarian cancer are rarely cured. However, the cure rate for advanced ovarian cancer is 20%, and there is emerging evidence that the rate can be improved by aggressive debulking surgery followed by intraperitoneal chemotherapy [15]. If scientists and science funders continue to focus on drugs given at end of life with the hope of extending progression-free survival, the capacity of the oncology community to undertake novel studies of adjuvant therapies with cure in mind could diminish. In the case of olaparib, patient advocacy groups, universities, drug companies, and commercial genetics laboratories are all aligned in the quest to create value for a drug that doesn't prolong survival. Nixon did not mince words. The goal of research in ovarian cancer is to improve the cure rate, and we should not be distracted from that goal.

CONFLICT OF INTEREST DISCLOSURES

I have read and understood *Current Oncology*'s policy on disclosing conflicts of interest, and I declare that I have none.

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