February 5, 2019 • Volume 41, Number 3

oncology-times.com

ONCOLOGY TIMES®

Independent News on HEMATOLOGY / ONCOLOGY

Report Highlights Drop in Cancer Deaths, Outlines Areas to Improve

BY PEGGY EASTMAN

Over the past 25 years, there has been a 27 percent drop in the overall U.S. cancer death rate, which translates into about 2.6 million fewer cancer deaths between 1991 and 2016. These statistics are contained in a new report from the American Cancer Society (ACS), "Cancer statistics, 2019," which was published early online in *CA: A Cancer Journal for Clinicians* (2019; doi:10.3322/caac.21551). The ACS also released a consumer version, "Cancer Facts & Figures 2019."

"We have made stunning progress against cancer and the 27 percent decline in the overall death rate over the last 25 years is a testament to that success," commented ASCO President Monica M. Bertagnolli, MD, FACS, FASCO, in a statement on the report. But the

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Talazoparib in Advanced Breast Cancer With a Germline *BRCA* Mutation

BY RICHARD SIMONEAUX

The presence of mutations to the *BRCA1* and/or *BRCA2* genes are associated with a number of disease states, including breast and ovarian cancers, as well as Fanconi anemia. Both genes encode proteins associated with the repair of DNA double-strand breaks. As a result, cancers driven by mutations in one or both of these genes may have greater susceptibility to therapies that generate double-strand DNA breaks, such as ionizing radiation, or those which inhibit the cell's ability to repair damaged DNA, such as platinum-based agents or PARP inhibitors.

CME/CNE Article

The first PARP inhibitor to receive FDA approval was olaparib, which, in December 2014, was cleared for the treatment of advanced ovarian cancer patients having a germline *BRCA* mutation (gBRCAm) with three or more prior lines of chemotherapy. Talazoparib, another PARP inhibitor, is currently being evaluated in EMBRACA (NCT01945775), a phase III clinical trial with advanced breast cancer patients having germline *BRCA1/2*

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More Accurate Leukemia Diagnosis Expected as Researchers Refine Classification

Like cartographers completing a map, investigators have identified multiple new subtypes of the most common childhood cancer—research that will likely improve the diagnosis and treatment of high-risk patients. St. Jude Children's Research Hospital scientists led the study, which appeared as an advance online publication in *Nature Genetics* (2019; doi:10.1038/s41588-018-0315-5).

Researchers used integrated genomic analysis, including RNA sequencing, to define the genomic landscape of B-cell acute lymphoblastic leukemia (B-ALL) in almost 2,000 children and adults. B-ALL is the most common form of ALL and the most common cancer in children. B-ALL remains the leading cause of pediatric cancer death.

Investigators identified 23 subtypes of B-ALL, including eight new subtypes, with distinct genomic and clinical features as well as outcomes. Subtype prevalence often varies with age. More than 90 percent of B-ALL cases can now be categorized by subtype compared with 70 percent a few years ago.

"B-ALL has remarkable molecular diversity, which we and others have used to refine classification and drive the development of precision medicines to improve B-ALL treatment and outcomes," said corresponding author Charles Mullighan, MBBS, MD, a member of the St. Jude Department of Pathology. "Part of precision medicine is an accurate molecular diagnosis, which this study provides to more patients."

Novel Subtype-Defining Alteration

Alterations of the transcription factor gene *PAX5* defined two new subtypes,

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mutant-driven disease; recently, results from this clinical study were published (*N Engl J Med* 2018;379:753-763).

One of the leading clinical investigators on this study was Jennifer K. Litton, MD, Associate Professor in the Department of Breast Medical Oncology at the University of Texas MD Anderson Cancer Center. Regarding the study results, Litton noted, "A statistically significant improvement was noted in progression-free survival (PFS) for those patients in the talazoparib arm of the study."

Citing the results obtained in this trial, the FDA granted approval in October 2018 for the use of talazoparib in patients with locally advanced or metastatic breast cancer with HER2-, gBRCAm-driven disease. Patient selection for this therapy is based upon confirmation using the FDA-approved companion diagnostic.

PARP Inhibitors

One of the main roles for the PARP family of proteins is to repair single-strand DNA breaks, or "nicks," which routinely occur during normal cellular activities. If these breaks are not corrected, when DNA replication occurs, double-strand DNA breaks can be produced by the cellular machinery. Accumulation of these double-strand DNA breaks can ultimately result in cell death.

As a result of *BRCA*-mutant driven disease possibly having heightened sensitivity to therapies that cause double-strand breaks or impair DNA repair processes, the use of PARP inhibitors against these malignancies was thought to be a viable strategy. In addition to inhibiting the enzyme's catalytic repair of single-strand DNA breaks, some PARP inhibitors may exert tumor killing effects via a separate mechanism—the trapping of PARP at sites of DNA damage.

However, these two activities appear to be distinct, as there does not appear to be a correlation between enzyme inhibition and PARP-trapping efficiency. Preclinical studies have indicated that the PARP-trapping may be an even greater contributor to cell death than the inhibition of enzymatic catalysis (*Cancer Res* 2012;72:5588-5599).

In preclinical studies, talazoparib displayed potent *in vitro* PARP enzymatic inhibition, with a half-maximal inhibitory concentration (IC_{50}) of 4 nM. This compound also showed proficient PARP-trapping potential, with an ability that was roughly 100-fold greater than that of other PARP inhibitors currently being investigated clinically (*Mol Cancer Ther* 2014;13:433-443).

As previously stated, in 2014, olaparib was the first inhibitor of this class to receive FDA approval for treating a mutant-*BRCA*-driven malignancy. Subsequently, rucaparib was granted accelerated approval by the FDA in December 2016 for previously treated *BRCA*-mutant ovarian cancer. In April 2018, this was then modified to regular approval as maintenance therapy for platinum-treated ovarian cancer patients that had either partial or complete response to that chemotherapy. Another compound in this class, niraparib, received FDA approval in March 2017 as a maintenance therapy for adult recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer patients who had prior complete or partial response to platinum-based chemotherapy.

EMBRACA Study

EMBRACA is an open-label phase III study evaluating the safety and efficacy of talazoparib in patients with either metastatic or treatment-resistant locally advanced breast cancer. When asked about the trial's design, Litton stated, "This was a 2:1 randomized trial of once daily talazoparib compared to a physician's choice chemotherapies (single-agent capecitabine, eribulin, gemcitabine, or vinorelbine) for patients with gBRCAm-driven, metastatic breast cancer."

Among the key inclusion criteria were the following:

- 18 years or older;
- metastatic or locally advanced, treatment-resistant breast cancer;
- suspected or centrally confirmed gBRCAm;
- received no more than three prior cytotoxic therapies for advanced breast cancer;
- had prior therapy with a taxane, an anthracycline, or both (unless treatment was contraindicated); and
- prior neoadjuvant or adjuvant platinum-based therapy (if patient had a disease-free interval for 6 months or more after the last dose).

Those patients who had objective disease progression while receiving platinum-based therapies for advanced breast cancer were excluded from participation in this study. Additionally, patients with HER2+ breast cancer were ineligible for participation in this trial.

It is of interest to note that no limit was placed upon the number of hormone-based treatments for those patients having HR+ disease. To be eligible for participation in this study, patients having central nervous system (CNS) metastases had to meet the following criteria: completion of definitive local therapy; stable CNS-based lesions, as shown by subsequent imaging; and required either no or low-dose glucocorticoid therapy.

The primary study endpoint was radiologic PFS, as assessed by blinded independent central review. This was defined as time between randomization and the date of first documented radiologic progression according to RECIST version 1.1 or death from any cause, whichever occurred first.

Key secondary endpoints included overall survival (OS); objective response rate (ORR, defined as the rate of patients showing complete response [CR] or partial response [PR]); and clinical benefit rate at 24 weeks (CBR, defined as the rate of patients showing CR, PR, or stable disease [SD] at 24 weeks or longer). Safety outcomes were assessed by adverse events (AEs) that were graded using NCI Common Terminology Criteria for Adverse Events, version 4.03.

In addition, patient-reported quality-of-life outcomes were assessed using the European Organization for Research and Treatment

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Learning Objectives for This Month's CME Activity:

After participating in this CME/CNE activity, readers should be better able to: 1. Summarize the purpose and design of the EMBRACA phase 3 evaluation of talazoparib in advanced breast cancer patients with a germline BRCA mutation. 2. Outline the findings and implications of this study.

Disclosure: The author(s), faculty, staff, and planners, including spouses/partners (if any), in any position to control the content of this activity have disclosed that they have no financial relationships with, or financial interests in, any commercial companies relevant to this educational activity.

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of Cancer (EORTC) Quality of Life Questionnaire (QLQ-C30) and the breast cancer-specific QLQ-BR23. Patient questionnaires were given at baseline, the initiation of each treatment cycle, and the end of treatment.

Eligible patients were randomly assigned in a 2:1 ratio to either the talazoparib or standard therapy group. Patients randomized to talazoparib received 1 mg orally QD continuously, with or without food, while the standard therapy group received protocol-specified chemotherapy (capecitabine, eribulin, gemcitabine, or vinorelbine) in continuous 21-day cycles, as specified by the institution's dose and regimen protocols. For each patient, the choice of standard therapy drug was determined prior to randomization. Standard therapy patients experiencing disease progression were not permitted to crossover to talazoparib.

Diagnostic imaging (CT, MRI, and nuclear-medicine bone imaging) was performed at baseline, every 6 weeks until week 30, and then every 9 weeks after that. Imaging of the head was repeated during the trial as clinically indicated, while bone imaging was done every 12 weeks after week 30. Central review was done by two radiologists for all tumor imaging; an adjudication assessment was done in accordance with the central imaging charter in cases of disagreement regarding disease progression.

Stratification of patients was performed using a number of factors, including number of prior cytotoxic chemotherapy regimens for advanced disease (0 vs. 1-3), hormone-receptor status (triple-negative vs. HR+), and CNS metastasis history (yes or no).

Results

From October 2013 to April 2017, 431 patients which comprised the intention-to-treat population were randomized at 145 sites in 16 countries. From this population, 287 patients were assigned to the talazoparib group and 144 were assigned to the standard therapy group. A total of 18 patients were randomly assigned to standard therapy group and one patient in the talazoparib group withdrew consent prior to receiving their investigational drug. For the standard therapy group, the breakdown by therapy was as follows: capecitabine, n=55 (43.7%); eribulin, n=50 (39.7%); gemcitabine, n=12 (9.5%); and vinorelbine, n=9 (7.1%). The date of data cutoff was Sept. 15, 2017.

Efficacy

The calculated median duration of follow-up, based on the reverse Kaplan–Meier estimator for PFS, was 11.2 months. After 269 cases of PD or death were confirmed by blinded independent central review, radiologic PFS was assessed. The median PFS for talazoparib group patients (8.6 months [95%CI: 7.2-9.3 months]) compared favorably to the figure obtained for those in the standard therapy group (5.6 months [95% CI: 4.2-6.7 months]). This provided a hazard ratio for disease progression or death of 0.54 (95% CI: 0.41-0.71; p<0.001). Independent review showed that after 1 year, 37 percent of the patients in the talazoparib group and 20 percent of the patients in the standard therapy group did not experience disease progression or death. It is of interest to note that the HR for disease progression or death that was determined by independent review matched the figure obtained by investigator assessment (0.54 [95% CI: 0.42-0.69]).

The risk of disease progression was lower for those in the talazoparib group than for the standard therapy group across all clinically relevant subgroups. The only subgroup which had a 95 percent confidence interval with an upper bound exceeding 1.0 was for those having prior platinum-based chemotherapy.

As of the primary analysis date, a total of 163 patients had died—108 in the talazoparib group and 55 in the standard therapy group. At interim analysis, the median OS was 22.3 months (95% CI: 18.1-26.2 months) and 19.5 months (95% CI: 16.3-22.4 months) in the talazoparib and standard therapy groups respectively, affording a hazard ratio for death of 0.76 (95% CI: 0.55-1.06; p=0.11).

The investigator-assessed ORR was 62.6 percent (95% CI: 55.8-69.0%) for those in the talazoparib group and 27.2 percent (95% CI: 19.3-36.3%) for the standard therapy group patients. A CR was noted in 5.5 percent of the talazoparib patients, while none in the standard therapy group had such a response.

The CBR at 24 weeks was 68.6 percent (95% CI: 62.9-74.0%) in the talazoparib group, which compared favorably to the 36.1 percent (95% CI: 28.3-44.5%) obtained for the standard therapy group.

Safety

The most commonly observed AEs in the talazoparib group were anemia, fatigue, and nausea, while in the standard therapy group, nausea, fatigue, and neutropenia were most prevalent. Grade 3 or 4 hematologic AEs were noted in 55 percent and 38 percent of the talazoparib and standard therapy patients, respectively. Grade 3 non-hematologic AEs occurred in 32 percent of the talazoparib group patients and in 38 percent of the standard-therapy group patients.

AEs that resulted in drug discontinuation occurred in 5.9 percent of talazoparib patients and in 8.7 percent of the standard therapy patients. AEs that necessitated dose modification (i.e., either reduction or interruption) occurred in 66 percent of the talazoparib group and 60 percent of the standard therapy group.

Serious treatment-related AEs were observed in 9 percent of the talazoparib and standard therapy patients, with anemia and neutropenia being the most prevalent in the talazoparib and standard therapy groups, respectively.

Patient-Reported Outcomes

In patient-reported outcomes, significant improvement was observed in the estimated overall mean change from baseline in the EORTC QLQ-C30 for the talazoparib group (3.0 [95% CI: 1.2-4.8]), in contrast to the significant deterioration in the standard therapy group (−5.4 [95% CI, −8.8 - −2.0]; p<0.001). Unlike standard therapy, treatment with talazoparib provided a significant delay in the onset of clinically relevant deterioration, as assessed by the global health status–quality-of-life scale.

Statistically significant improvement was noted for the talazoparib group (−5.1 [95% CI, −6.7 - −3.5]) in the estimated overall mean change from baseline in the breast cancer-specific QLQ-BR23. In contrast, a nonsignificant change was obtained for the standard therapy group (−0.1 [95% CI: −2.9 - 2.6]; p=0.002). As with the global health status–quality-of-life assessment, QLQ-BR23-based patient reported outcomes also showed that relative to the standard therapies, treatment with talazoparib resulted in a significant delay in the onset of clinically relevant deterioration.

Discussion

When asked why patients without germline *BRCA1/2* mutations were excluded from this study, Litton replied, "At this point, there is not strong evidence of benefit from single-agent PARP inhibitors in metastatic breast cancer in patients without changes in *BRCA* genes."

In noting the prominent results in this study, she stated, "The study did meet its primary endpoint, but the patient-reported outcomes were also very intriguing, with improvement in quality of life and decreased time to meaningful health deterioration compared with those patients who received chemotherapy."

Regarding the implications of this trial's results for treating breast cancer patients with germline *BRCA1/2* mutations, Litton commented, "This study is the second phase III randomized trial of PARP inhibitors for these patients, both showing efficacy; so yes, the use of PARP inhibitors is a change in the standard of care for these patients." As a result of the findings obtained in this study, on Oct. 16, 2018, the FDA granted approval for the use of talazoparib for the treatment of locally advanced or metastatic HER2-, gBRCAm-driven breast cancer.

When asked about additional studies being undertaken for PARP inhibitors, Litton noted, "Further studies are ongoing to see if novel combinations can expand talazoparib's activity in other breast cancer patients. There are multiple ongoing studies evaluating combinations with other targeted therapies and/or immunotherapy. In addition, the NeoTALA trial is evaluating the use of talazoparib in the neoadjuvant setting," she concluded. OT

Richard Simoneaux is a contributing writer.