Hormone Receptor–Positive, HER2-Negative Breast Cancer: Recent Advances and Best Practices

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Presenters' disclosures of conflicts of interest are found at the end of this article.

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Abstract

Lee Schwartzberg, MD, FACP, and Heather Greene, MSN, FNP, AOCNP®, reviewed optimal therapy for patients with hormone receptor–positive, HER2-negative breast cancer, as well as the management of adverse events associated with treatment.

Approximately 70% of patients with metastatic breast cancer have hormone receptor–positive, HER2-negative disease, and nearly 30,000 patients die from this disease each year, but there has been a marked change in treatment over the past 5 years. CDK4/6 inhibitors have transformed the approach to therapy along with the identification of relevant biomarkers such as those related to *BRCA* and *PIK3CA* gene mutations. At JADPRO Live 2019, Lee Schwartzberg, MD, FACP, and Heather Greene, MSN, FNP, AOCNP®, of West Cancer Center and Research Institute in Memphis, Tennessee, discussed the selection of optimal therapy for patients with hormone-positive, HER2-negative breast cancer in accordance with evidence-based treatment recommendations, as well as the selection of therapy based on the presence of relevant biomarkers. The clinicians also discussed the management of adverse events associated with treatment and the clinical significance of emerging data in the field.

"Molecular profiling is coming of age in breast cancer, and next-generation sequencing is now being recommended in other tumor types at the time of diagnosis," said Dr. Schwartzberg, Medical Director of the West Cancer Center in Memphis, Chief Medical Officer for One Oncology, and Professor of Medicine at the University of Tennessee Health Science Center. "Next-generation sequencing, at some point in the journey of a hormone receptor–positive metastatic breast cancer patient, makes sense and will help drive decisions for you."

CDK4/6 INHIBITORS

As Dr. Schwartzberg explained, CDK4/6 inhibitors, a class of drugs

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that target particular enzymes called CDK4 and CDK6 have been a tremendous breakthrough in the past 5 years. Three agents have been approved by the U.S. Food & Drug Administration: palbociclib, ribociclib, and abemaciclib. All three drugs are indicated for initial endocrine-based therapy in postmenopausal women with an aromatase inhibitor (ribociclib is recommended with fulvestrant or an aromatase inhibitor) and also for disease progression following endocrine therapy with fulvestrant (Table 1).

Data from the first-line trials of CDK4/6 inhibitors with a nonsteroidal aromatase inhibitor in hormone receptor–positive, HER2-negative metastatic breast cancer demonstrated similar Kaplan-Meier curves across three separate trials, each with slightly different criteria of inclusion and exclusion (Finn et al., 2016; Goetz et al., 2017; Hortobagyi et al., 2018).

"Some differences make cross-trial comparisons difficult, but all three trials show an approximately 10-month improvement in median progression-free survival with the addition of the CDK4/6 inhibitor vs. standard therapy of nonsteroidal aromatase inhibitor in patients who are receiving their first endocrine therapy for metastatic breast cancer," said Dr. Schwartzberg.

Moreover, said Dr. Schwartzberg, despite multiple lines of endocrine therapy and chemotherapy for these patients, updated overall survival data also showed a 30% improvement for ribociclib compared to placebo and endocrine therapy (Im et al., 2019).

"If you're going to see this kind of impact down the line for these patients, first-line therapy with a CDK4/6 inhibitor might make sense," said Dr. Schwartzberg, who noted that these agents offer improvement from a quality-of-life perspective, as well. "Patients with metastatic breast cancer don't just want to live longer; they want to live a good quality of life."

TOXICITIES AND MANAGEMENT FOR CDK4/6 INHIBITORS

As Ms. Greene explained, CDK4/6 inhibitors are generally well tolerated, with most toxicities being hematologic and gastrointestinal. Nevertheless, there are some difference among the three approved agents. Palbociclib and ribociclib are associated with higher rates of grade 3 and 4 neutropenias, said Ms. Greene, and abemaciclib is associated with higher rates of grade 3 and 4 diarrhea. Ribociclib is also the only CDK4/6 inhibitor that has an increased risk of QTc prolongation. Finally, all three agents can cause some mild elevation in liver enzymes (Table 2).

"With abemaciclib, diarrhea typically occurs quickly," said Ms. Greene, who noted that manufacturers initially provided samples of loperamide with starter packs of abemaciclib. "That being

Table 1. CDK4/6 Inhibitors

HR+/HER2– advanced or metastatic breast cancer	Palbociclib	Ribociclib	Abemaciclib
Initial endocrine-based therapy in postmenopausal women	With AI	With fulvestrant or AI	With AI
Initial endocrine-based therapy in pre-/perimenopausal women	–	With AI	–
With disease progression following endocrine therapy	With fulvestrant	With fulvestrant	With fulvestrant As monotherapy
Dose/schedule	21 days on, 7 days off (28-day cycle)	21 days on, 7 days off (28-day cycle)	Continuously until disease progression or unacceptable toxicity
Dose frequency	Once daily	Once daily	Twice daily
With/without food	With	With or without	With or without

Note. HR = hormone receptor; HER2 = human estrogen receptor 2; AI = aromatase inhibitor. Information from Eli Lilly and Company (2019); Novartis (2020); Pfizer (2019).

Table 2. Common Toxicities of CDK4/6 Inhibitors

		Neutropenia			Diarrhea		
Drug	**Trial**	**All grades**	**Grade 3**	**Grade 4**	**All grades**	**Grade 3**	**Grade 4**
Palbociclib + letrozole	PALOMA-2	80%	56%	10%	26%	1%	0%
Palbociclib + fulvestrant	PALOMA-3	83%	55%	11%	24%	0%	0%
Ribociclib + letrozole	MONALEESA-2	75%	50%	10%	35%	1%	0%
Ribociclib + fulvestrant	MONALEESA-3	69%	46%	7%	29%	< 1%	0%
Ribociclib + NSAI + goserelin	MONALEESA-7	78%	55%	10%	NR		
Abemaciclib monotherapy	MONARCH 1	37%	19%	5%	90%	20%	0%
Abemaciclib + fulvestrant	MONARCH 2	46%	24%	3%	86%	13%	0%
Abemaciclib + anastrozole or letrozole	MONARCH 3	41%	20%	2%	81%	9%	0%

Note. NSAI = nonsteroidal aromatase inhibitor. Information from Eli Lilly and Company (2019); Novartis (2020); Pfizer (2019).

said, as oncology advanced practitioners, we know how to manage diarrhea: loperamide, atropine and diphenoxylate, and the 'BRAT' diet. There are also dose reductions that we can consider."

According to Ms. Greene, neutropenia associated with CDK4/6 inhibitors can also be quite profound and differs significantly from neutropenia associated with cytotoxic chemotherapy. For grade 1 and 2 neutropenia, Ms. Greene advised monitoring the patient very closely. For grade 3 and 4 neutropenia, on the other hand, there will be dose reductions, interruptions, or delays. Nevertheless, said Ms. Greene, these patients almost never need a growth factor.

Finally, palbociclib and abemaciclib recently updated their package insert to include a risk for interstitial lung disease and pneumonitis.

"If you have patients coming in with worsening pulmonary symptoms, you need to pay attention to make sure that it is not pneumonitis," Ms. Greene cautioned. "If it is, that's a permanent discontinuation on both of these drugs" (Table 3).

NEXT TREATMENT: ALPELISIB PLUS FULVESTRANT

For patients with hormone receptor–positive, HER2-negative advanced breast cancer who progress on or after an aromatase inhibitor, the next option is alpelisib plus fulvestrant. As Dr. Schwartzberg reported, results of the SOLAR-1 trial showed progression-free survival in the *PIK3CA*-mutated cohort that was twice what it was than in the patients who received fulvestrant only (from 5.7 months to 11 months), and the number of patients with a measurable response doubled from 16% to 35%, as well (André et al., 2019).

Alpelisib was approved in combination with fulvestrant in patients with *PIK3CA*-mutated, hormone receptor–positive breast cancer in men or postmenopausal women following progression on endocrine therapy. According to Dr. Schwartzberg, however, clinicians still have the option for up to three rounds of endocrine therapy for these patients.

Regarding toxicities, Ms. Greene reported that the most common adverse reactions on alpelisib were diarrhea, nausea, stomatitis, fatigue, weight decrease, decreased appetite, and rash. In addition, 79% of patients on trial had hyperglycemia, which is not a toxicity clinicians are used to managing in the solid-tumor world, said Ms. Greene, who noted that clinicians must monitor fasting plasma glucose prior to starting therapy.

Diarrhea is another ongoing side effect, with 58% of patients developing some grade of diarrhea on the SOLAR-1 trial. Finally, said Ms. Green, alpelisib also carries a small risk for pneumonitis, which was reported in 1.8% of patients on trial.

PARP INHIBITORS

Because de novo *BRCA* mutations occur in metastatic breast cancer in approximately 3% to 5% of patients, a PARP inhibitor is another option for patients who are positive for the germline mutation. As Dr. Schwartzberg reported, there are two PARP inhibitors approved for germline-mutated

Table 3. Summary of Management of Nonhematologic Toxicities for CDK4/6 Inhibitors

CDK4/6 inhibitor	CTCAE grade	Dosage modifications
Abemaciclib	1 or 2	None required If grade 2 persists > 7 days, withhold until resolution to baseline or grade ≤ 1, then resume at next lower dosage
	3 or 4	Withhold until resolution to baseline or grade ≤ 1, then resume at next lower dosage
Palbociclib	1 or 2	None required
	≥ 3	Withhold until resolution to grade ≤ 1 or grade ≤ 2 if not a safety risk for patient, then resume at next lower dosage
Ribociclib	1 or 2	None required
	3	Withhold until resolution to grade ≤ 1, then resume at same dosage; if grade 3 recurs, resume at next lower dosage
	4	Discontinue ribociclib

Note. CTCAE = Common Terminology Criteria for Adverse Events. Information from Eli Lilly and Company (2019); Novartis (2020); Pfizer (2019).

BRCA. Studies showed an improvement in progression-free survival of approximately 45% for both PARP inhibitors and an 18% improvement in overall survival for these heavily treated patients (Litton et al., 2018; Robson et al., 2017). According to Dr. Schwartzberg, these response rates are much higher with either talazoparib or olaparib compared to chemotherapy.

"There is a bias sometimes that chemotherapy gives us the best response rate, but that's not true against CDK4/6 inhibitors, and it's not true against BRCA inhibitors," said Dr. Schwartzberg. "The biologic drugs give you better outcomes when compared head-to-head with chemotherapy, and these drugs are less toxic than chemotherapy."

Dr. Schwartzberg underscored the NCCN Guidelines that recommend testing for germline-mutated *BRCA* in patients with HER2-negative metastatic breast cancer. Insurance will cover this, said Dr. Schwartzberg, and this can be done before starting chemotherapy or even endocrine therapy. If patients don't have wild-type *PIK3CA* mutation or germline-mutated *BRCA*, they should get chemotherapy after two lines of therapy, he added. While germline *BRCA* mutations occur in 3% to 5% of hormone receptor–positive, HER2-negative metastatic breast cancer, somatic *PIK3CA* mutations occur in 30% to 40% patients with this disease.

"I would recommend giving a PARP inhibitor for germline *BRCA* mutation before chemotherapy based on the fact that the response rates were higher, progression-free survival was longer, and the toxicity was less," said Dr. Schwartzberg.

COMMON SIDE EFFECTS OF PARP INHIBITORS

As Ms. Greene reported, data from the OlympiAD trial showed that 97% of patients experienced some type of adverse event on the study. Most of these, however, were grade 1 or 2. In fact, said Ms. Greene, there were fewer grade 3 or 4 toxicities with olaparib than in the control arm (Robson et al., 2017).

The most common side effects of olaparib were anemia, neutropenia, nausea, vomiting, diarrhea, and fatigue. The only grade 3 or 4 toxicity greater than 10% was anemia, said Ms. Greene, who noted that while 35% of patients required dose delays or interruptions, only 5% of patients required permanent discontinuation.

"These safety data suggest that with appropriate management, dose interruptions, dose delays, or dose reductions, we can keep people on therapy and get them through this line of treatment," said Ms. Greene.

As Ms. Greene reported, side effects on talazoparib, the second PARP inhibitor, are similar to olaparib, with more than 50% of patients requiring dose reductions but only a very small amount requiring permanent discontinuation (Litton et al., 2018).

Finally, said Ms. Greene, given the risk of hematologic toxicity, a complete blood count should be tested at baseline and then monthly. With worsening cytopenias, however, Ms. Greene noted that this test could be performed more frequently.

Disclosure

Ms. Greene is on the speakers bureau for Pfizer, and Dr. Schwartzberg is a consultant for Amgen, AstraZeneca, Genentech/Roche, and Pfizer.

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