Disparities Watch:

Many Breast Cancer Patients in Appalachia Not Taking Prescribed Therapy, even with Insurance

BY HEATHER LINDSEY

Nearly a third of hormone-receptor positive breast cancer survivors in Appalachia are not taking their prescribed adjuvant hormone therapy to prevent recurrence, despite having insurance that would pay for it, according to new research (***Medicine 2015;94:e1071***).

"We found that a complex variety of factors including poverty, geography, and preventive health orientation affect the health of women with breast cancer in Appalachia," said lead author Rajesh Balkrishnan, PhD, Professor of Public Health Sciences at the University of Virginia School of Medicine.

Asked for his perspective, Ricardo H. Alvarez, MD, MSc, Director of Cancer Research and a breast medical oncologist at Cancer Treatment Centers of America, Southeastern Regional Medical Center, said the results reflect those of similar larger studies finding non-adherence to oral medications in chronically ill individuals, including cancer patients: "With close to 18 million cancer survivors in the United States by the year 2022, according to American Cancer Society statistics, adherence to oral adjuvant medication is going to become an increasingly important issue."

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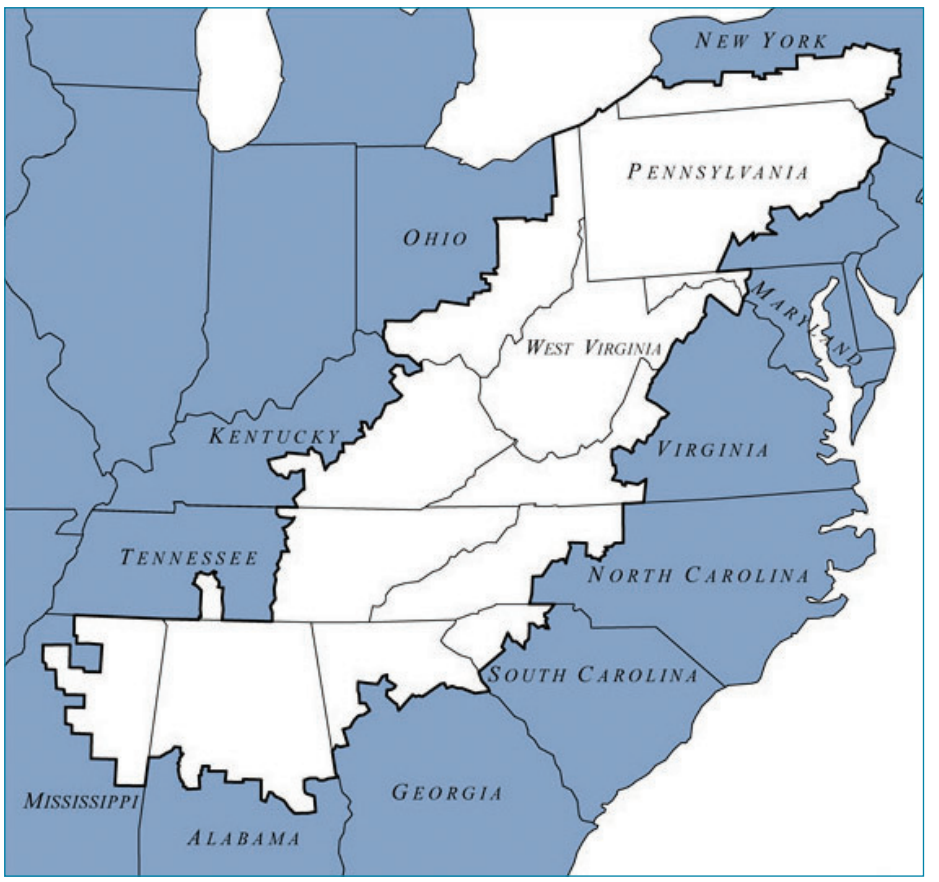

Study Details

For the retrospective cohort study, Balkrishnan and colleagues—first author is Xi Tan, PhD—analyzed information for the years 2006 to 2008 for female breast cancer survivors in the Appalachian region of Pennsylvania, Ohio, Kentucky, and North Carolina.

The team cross-referenced cancer registries with Medicare claims and other sources of data, including the Appalachian Regional Commission, the U.S. Census Bureau, and the National Center for Health Statistics, to identify 428 women with stages I to III hormone-receptor-positive breast cancer who received adjuvant endocrine therapy and assess patient characteristics.

Medication adherence was defined as the number of days for which the drug was dispensed divided by the number of days the drug was needed. Non-persistence was defined as discontinuation of the drugs after a gap of more than 60 days.

Approximately 31 percent of patients were non-adherent to adjuvant endocrine therapy, and 30 percent were non-persistent during an average follow-up of 421 days.

Overall, patients receiving catastrophic insurance coverage were three times more likely to adhere to their adjuvant endocrine therapy, and they also had a 44 percent lower risk of discontinuing therapy.

Notably, tamoxifen, relative to aromatase inhibitors (AIs), was associated with higher odds of adherence and a lower risk of non-persistence. Out-of-pocket drug costs, dual eligibility status, and coverage gaps all influenced AI adherence and persistence.

Using pain medication to manage side effects was significantly associated with poor adherence and persistence for AIs but not for tamoxifen. Non-adherence and non-persistence were also associated with all-cause mortality; and during the study period, all-cause death occurred in 3.5 percent of patients.

County-Level Data

The deficiencies in access to care in Appalachia were illustrated by county-level study data. For example, 43 percent of patients were categorized as being economically distressed, 67 percent lived in largely rural environments, and 88 percent experienced health care professional shortages.

Alvarez said that the number of descriptive characteristics of the study population that the researchers captured was valuable. For example, about eight percent of patients were younger than 65 when diagnosed, 56 percent had stage I disease, 39 percent had mastectomies, and 50 percent had chemotherapy. Notably, about 90 percent of patients did not take antidepressants or painkillers, which may indicate that this group was not open to taking any type of oral medication, he said.

Reasons for Noncompliance

Balkrishnan said that adjuvant endocrine therapy-induced side effects such as musculoskeletal pain may increase the physical burden on patients, cause misbeliefs about the use of these medications, and adversely affect patients' intentions to adhere—and this may be a bigger problem in a region with both geographical and socioeconomic disparities such as Appalachia.

Also asked for her perspective, Marleen Meyers, MD, Director of the Perlmutter Cancer Center Survivorship Program at NYU Langone Medical Center, said that while aromatase inhibitors can cause significant joint pain and stiffness, most of the patients in this study were older than 65 and may therefore have already had joint

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pain associated with arthritis—"adding insult to injury." Moreover, living in a rural area may create more demands for physical labor, also contributing to poorer tolerance and acceptability of joint pain.

In geographically remote regions where ready access to a doctor or nurse practitioner isn't available, patients may simply stop taking their medication if questions arise about its use or if they start experiencing side effects. In addition, filling prescriptions in rural areas can often be challenging because of what may be long distances to the nearest pharmacy.

Also affecting both compliance and persistence are the costs of AIs and their related side effects, which sometimes include the need for prescription pain medications, said Bhuvaneswari Ramaswamy, MD, Associate Professor in the Division of Medical Oncology and a breast cancer clinical researcher at Ohio State University Comprehensive Cancer Center—Arthur G. James Cancer Hospital and Richard J. Solove Research Institute.

Another factor is the amount and type of insurance coverage patients have to cover these costs. Meyers added that while insurance typically covers most adjuvant hormone therapies, people in this study population may be watching every dollar. Tamoxifen is generally less expensive than AIs, but AIs are now off patent and are usually not cost-prohibitive, she said.

Notably, in this setting, medication is being used to prevent cancer recurrence—"which means you're treating something you can't see," she continued.

If patients don't fully understand why they are taking adjuvant hormone therapy, compliance often becomes a problem. "It's not like diabetes, where you measure high blood sugar, and then take a medication and see lower levels. It can be a leap of faith for patients as to why they're taking hormone therapy."

This is not the first study that has shown that non-adherence to adjuvant hormone therapy impacts all-cause mortality, Ramaswamy noted. Breast cancer patients who aren't taking their hormone therapy may not be compliant

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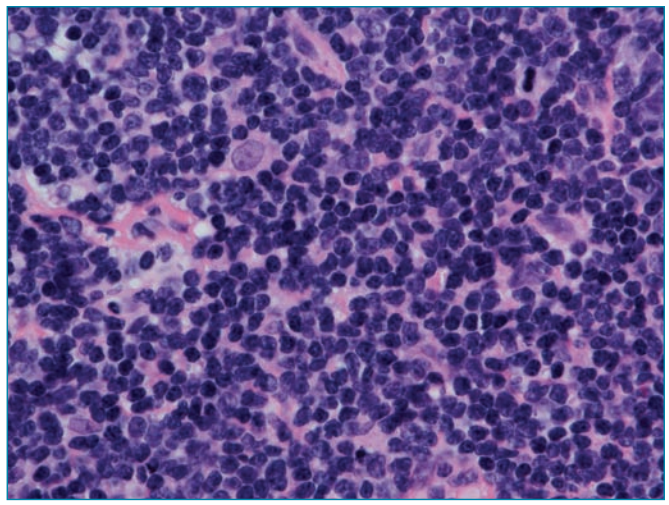
MCL: Follow-Up Confirms Ibrutinib's Benefits in Relapsed/Refractory Disease

BY HEATHER LINDSEY

Ibrutinib continues to provide patients with relapsed or refractory mantle cell lymphoma (MCL) with durable responses and a manageable safety profile, according to longer-term follow-up from an international, multicenter, open-label, Phase II trial published in *Blood* (***2015;126:739-745***).

The drug already received accelerated approval in that group based on the results published two years ago in the *New England Journal of Medicine* (***2013;369:507-516***). "Ibrutinib is the best medicine for mantle cell lymphoma so far," said Michael Wang, MD, the lead author of both studies and Professor in the Department of Lymphoma/Myeloma at the University of Texas MD Anderson Cancer Center. "It is now used in almost every patient who has received frontline therapy and has relapsed."

> "Ibrutinib is one of the easiest treatments to give to patients compared with other therapies we use for MCL."
> —*Michael Wang, MD*



Mantle Cell Lymphoma

Ibrutinib for the treatment of mantle cell lymphoma is "a hot topic in terms of new therapeutics for our patients," commented Paul Barr, MD, Director of the Clinical Trials Office at Wilmot Cancer Institute at the University of Rochester (NY) Medical Center. "Most lymphoma experts agree that the drug is very promising."

Mantle cell lymphoma can be aggressive and incurable, as well as difficult to study because of the relatively low number of cases, he explained. "When we see agents like ibrutinib that provide promising results and are well tolerated, it gets everyone's attention."

The new study—a follow-up to results reported at the most recent American Society of Hematology Annual Meeting—shows a sustained benefit beyond two years, with a well-tolerated side effects profile that is perhaps even better compared with other available drugs such as bortezomib and lenalidomide for patients with previously treated MCL, said Jack Jacoub, MD, a medical oncologist at MemorialCare Cancer Institute at Orange Coast Memorial Medical Center in Fountain Valley, California. Bruton tyrosine kinase, which ibrutinib inhibits, "is a very active and targetable" pathway.

Study Details

The median follow-up time of the updated study was 26.7 months. Patients were a median 68 years old and had a median of three previous therapies.

Patients who had a response or stable disease were eligible for long-term extension, in which the median treatment was 8.3 months. Fifty-one individuals (46%) were treated for more than a year, and 22 (20%), took ibrutinib for more than two years. The most common reasons for discontinuation were disease progression (56%), adverse events (11%), withdrawing consent (5%), and a physician's recommendation (3%).

The overall response rate (ORR) was 67 percent, and 23 percent of patients had a complete response (CR). Similarly, in the original *NEJM* study, patients with MCL had an ORR of 68 percent and a CR of 21 percent.

In the updated analysis, the median duration of response was 17.5 months. The median time to initial response was 1.9 months, while the median time to CR was 5.5 months.

In 48 patients who had received prior bortezomib, ORR was 65 percent, and in 27 patients who had received previous lenalidomide, ORR was 59 percent. The 24-month progression-free survival (PFS) rate was

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with taking medications for other comorbidities, which could also be contributing to the danger.

And, said Balkrishnan, with the increasing trend toward patient-centered medicine, physicians should explore whether they can empower patients to take better care of themselves. Cancer care professionals need to find a way to decrease any type of mortality threat in individuals who have been successfully treated for a malignancy.

Possible Solutions

Patient education that explains exactly what oncologists are trying to achieve with these medications is crucial for combating noncompliance, Meyers noted. Patients also need to fully understand what side effects they can expect when taking these drugs.

Having a way to identify individuals who have a high risk of discontinuing their medications would help oncologists to better target patient education and provide consistent follow-up to women who need it the most, Ramaswamy said.

Patients need frequent follow-up with a physician or nurse for monitoring and to discuss their care, Meyers said. "If people have a place to go and report how they're feeling, we get better compliance—often because changes can be made to mitigate side effects."

> "Cost-effective options in telemedicine and mobile health technologies may help bring state-of-the-art cancer care to the region."

Nurses and care managers also need to routinely check the patient's number of pharmacy refills and call to ensure she is taking the right drug, at the right doses, at the right time, and on the right schedule, Alvarez said. In addition, since polypharmacy is so common in older individuals, health care providers need to check whether patients have started taking any other medications that may interact with the adjuvant hormone therapy.

Health care providers also need to find innovative ways to improve access to care for populations who may need it the most. For example, said Balkrishnan, cost-effective options in telemedicine and mobile health technologies may be a way to provide state-of-the-art oncology care to the Appalachian population.

Additionally, the use of patient navigators needs to be explored more in this setting, he said. Mobile health clinics and improving awareness of preventive health are other approaches that may help to improve compliance.