Investigating Metformin for ER-Positive Breast Cancer

BY MICHELLE PERRON

As one of the most prescribed and studied medications over the past 20 years, metformin has a fairly gilded reputation. This biguanide, derived from the French lilac, is the most prescribed anti-diabetes drug worldwide. It has an excellent safety profile and is well-tolerated. It’s also a popular focus worldwide. It has an excellent safety profile and is well-tolerated. It’s also a popular focus of cancer research, due to its ability to prevent protein synthesis and cell growth, and to activate AMPK to stop the cell cycle.

In 2020, approximately 200 randomized clinical trials are investigating metformin as a potential cancer treatment agent. The groundwork for these trials was laid by numerous studies that identified potential applications in the prevention or treatment of multiple types of cancer. But a caution flag is being waved when it comes to estrogen receptor-positive

Collaboration at All Levels Informs Care, Trials & Patient Outcomes

BY VALERIE NEFF NEWITT

Rosin M. Connolly, MB, BCh, MD, has a message for fellow oncology researchers and clinicians. “Collaborative, patient-oriented work is vital to making a difference in cancer. We have many patients who are willing to give us their time and insights into their experiences. Many patient advocates who are very experienced on the research side can guide us in our studies. We need to listen to all those around us,” said the medical oncologist, now at Cork University Hospital in Ireland after an impressive 10-year stint at Johns Hopkins in Baltimore. She is also the Professor Gerald O’Sullivan Chair in Cancer Research at University College Cork (UCC), Ireland. “Patient advocates are very strong in breast cancer, and certainly they’ve helped me along the way,” she said with humility. “More and more, there’s a realization that we need to have patients at the table at many levels for developing studies and at oncology meetings to give their perspective. Otherwise, we can lose sight of what’s really important to them.”

Prior to returning to her native Ireland, Connolly was Associate Professor of Oncology and Co-Director of the Developmental Therapeutics Program at Johns Hopkins in Baltimore. She is also the Professor Gerald O’Sullivan Chair in Cancer Research at University College Cork (UCC), Ireland. “Patient advocates are very strong in breast cancer, and certainly they’ve helped me along the way,” she said with humility. “More and more, there’s a realization that we need to have patients at the table at many levels for developing studies and at oncology meetings to give their perspective. Otherwise, we can lose sight of what’s really important to them.”

Case Study: Boggy Head Syndrome

BY ABDUL RISHI, MD, JACQUELINE FAIRCCHILD, MD, & WILLIAM LOGAN, MD

Patients with sickle cell disease often present to the emergency department for pain crises. The usual management is conservative, including admission to the hospital, intravenous fluids, and pain control. Herein, we describe a very intriguing and unusual case of a painful complication of sickle cell disease that may present a diagnostic dilemma to even the most astute clinician. We have also highlighted the key points of the complication, the utility of specialized investigations and ultrasound, and the need to use antibiotics judiciously while being an antibiotic steward.

Sickle cell disease is a relatively common inherited disorder of the hemoglobin among individuals of African descent. The abnormal hemoglobin causes red blood cells to “sickle” under low oxygen tension leading to capillary occlusion. This can lead to a multitude of complications. Central nervous system complications such as the more common cerebral ischemia and stroke and the less common dural venous sinus thrombosis and hemorrhage (J Neurosurg Pediatr 2009;4(6):532-535) are rather the “do not miss” complications as delaying early therapy can be potentially life threatening.

A 19-year-old male with history of sickle cell disease, acute chest syndrome, and avascular necrosis of the head of the femur presented with acute onset, severe headache associated with nausea, vomiting, and dizziness. He described his headache as throbbing in the crown of his head with intermittent stabbing. He felt this was like his previous sickle cell crises pain. He denied any numbness, weakness, tingling, and
the Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins where she continues to have an adjunct position. As noted in her UCC bio, she gained “expertise in the development of biomarkers of response to anti-cancer therapies, and the design and conduct of clinical trials that test investigational drugs in the treatment of patients both in early and late stages of cancer.”

She continues as study chair for the international phase III E2112 study from the Eastern Cooperative Oncology Group (ECOG) and the American College of Radiology Imaging Network (ACRIN) research group, which is investigating the epigenetic agent entinostat in combination with hormonal therapy in patients with metastatic breast cancer. Her work earned her the prestigious ECOG-ACRIN Young Investigator Award for excellence in clinical investigation in 2019.

**Breakthrough Designation**

Explaining the rationale behind this randomized trial of endocrine therapy plus entinostat or placebo in both women and men with hormone receptor-positive advanced breast cancer, Connolly said, “Despite many advances in the treatment of advanced breast cancer that is hormone receptor-positive, unfortunately, many patients do not respond to treatment and have disease progression. So we are trying to identify strategies to overcome resistance to this hormonal therapy. One possibility may be with the use of histone deacetylase (HDAC) inhibitors, a class of drugs found to overcome endocrine resistance in pre-clinical models.”

Connolly noted that, in an earlier randomized phase II study, the HDAC inhibitor entinostat in combination with the hormonal therapy exemestane in patients with advanced breast cancer was evaluated. “What was most interesting—and unexpected—was an overall survival benefit of approximately 8 months favoring the entinostat arm. This led the FDA to designate entinostat as a ‘breakthrough therapy’ in combination with exemestane. This breakthrough designation allowed us to move forward rapidly with the phase III study, which required FDA approval because it is a registration trial.”

The primary objective of the subsequent 600-patient phase III study, which completed accrual last year, was to look for both improvements in progression-free survival and/or overall survival with use of entinostat versus placebo. Even though this study was put on a “fast track,” it has taken the researchers many years to get to this pivotal point from initial development of the study. The team is currently waiting maturation of the study results.

Connolly did reveal, however, that this combination therapy has been well-tolerated by patients, so if it shows improved survival outcomes it may lead to an important new treatment option for patients with advanced breast cancer.

**On the Personal Side**

Born and raised in Dublin, Connolly said she came to her interest in cancer care, when she was younger. I had hospital admissions with asthma exacerbations and, to be honest, I found that I really just loved being in the hospital, she recalled. “I just have these great memories of going to ‘school’ in the hospital classroom and talking to the wonderful nurses. It was a very positive experience for me and helped me make the decision to go into medicine.”

Connolly eventually went to Trinity College Dublin (“…which is right in the center of Dublin, a fantastic location, in the middle of all the activity…” ) and rotated through a medical oncology service in a large city center teaching hospital. “One of the physicians I trained with, a breast cancer expert, had trained at Johns Hopkins and spoke very highly of it and the opportunities there. So I just moved along that path, going through the internal medicine training first, and then to Hopkins to complete my oncology fellowship training.”

She moved to Baltimore about 11 years ago and stayed for just over a decade. Now married to a fellow Irishman and mother of four children, Connolly and family have moved back to Cork, the second largest city, in the south of Ireland. “Having children, there was definitely a pull to bring them back to their extended family in Ireland,” she said. “But we really enjoyed living in Baltimore, and in fact the children really miss it; my 7-year-old talks about Baltimore all the time.”

**Spotlight on Young Investigators**

**Finding Her Path**

While at Hopkins, Connolly decided to make breast cancer a focus of her work. “I had exposure to patients with breast cancer early on, and I enjoyed taking care of them,” she noted. “I think there are very specific needs that patients with breast cancer have. Many are young with young families. They face so many commitments while trying to juggle their disease and treatment.”

Additionally, when she was at Hopkins, breast cancer research and treatment was rapidly evolving. “Breast cancer led the field in terms of new drug development for quite some time, just as lung cancer and melanoma have done in recent years with the explosion of immunotherapy, for example,” said Connolly. “But for many, many years, breast cancer was where it was happening in terms of understanding the biology of the disease, and the new treatments, and exciting advances. I grew up in that phase, while a lot of those treatments were being approved. One that I remember for example, was the approval of trastuzumab. I remember being at the ASCO meeting when those results were presented to the audience. It was just outstanding, the benefit that was being seen, and then the gasp from the audience. Breast cancer was very exciting at the time when I was training, and it still is.”

She credits Johns Hopkins, in part, for her status as a clinician researcher. “Academics and research are the bread and butter there,” she said. “But that’s not to say I think every oncologist has to do both. Some people are the most fantastic clinicians, and their drive and their desire is to be with the patients all the time. Other people thrive best by working in the lab and exploring the biology, genomics, immunology, etc. However, the clinical investigator path that I took offers the best of both worlds to me.

“I think it’s very important for clinical investigators to have their hand in the clinic because they are seeing the patients, understanding what the issues are, developing ideas, determining what’s important or not important. Then they can have interactions with basic scientists when they have ideas and vice versa. These collaborative interactions become productive brainstorming sessions across disciplines that help to move the field forward.”

**Facing Forward**

Today, Connolly looks to the future with two main goals in mind for her career. “I continue to hope to bring new treatments to patients, either through collaborations with industry, with cooperative groups like ECOG-ACRIN, or more homegrown ideas coming from interactions with our own basic scientists, developing what we call investigator-initiated studies,” she said. “That would involve developing clinical trials with new treatments for patients, such as the E2112 study that I described earlier.”

“The other goal is to work with existing treatments that we have,” she told Oncology Times. “How can we tailor a treatment better? We
have a lot of treatments that we can offer patients, but we know that each patient doesn’t necessarily benefit from everything that we give them. So how can we find out which patients will suit which treatments, and how do we individualize the decisions? That’s the field of predictive biomarkers where we’re testing the tumor samples, testing the blood, doing an imaging study, like a PET study, while trying to determine who will or won’t respond to a certain treatment.

One example of such a biomarker evaluation was the TBCRC026 study that Connolly published last year in the Journal of Clinical Oncology (2019;37(9):714-722).

“Working with newly diagnosed patients with HER2-positive breast cancer, we wanted to see if we could predict who might do well with HER2 therapy alone, without using chemotherapy. And it looks like we were able to predict in the phase II study who might benefit from the treatment, but in fact more precisely who might indeed need more aggressive approaches,” detailed Connolly.

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—Roisin M. Connolly, MB, BCh, MD, Professor at University College Cork in Ireland

“The most important finding was the change in the standardized uptake value (SUV) on the PET scan. We measured the SUV on a PET scan at baseline and again 2 weeks after starting treatment. What we found was that patients whose SUV declined more than 40 percent over that 2-week period were more likely to have a response to treatment. And those patients whose SUV did not decline by 40 percent were extremely unlikely to have what we call a pathological complete response (pCR) to the treatment. We were trying to determine who needed maybe a less-aggressive approach versus a more-aggressive approach. The study was reasonably unique in that it only used HER2 therapy without chemotherapy for the initial biomarker phase. Now we’re hoping to move that imaging biomarker into a larger study to try to validate those results.”

Connolly said she hopes to discover if there may be a group of patients who might benefit from HER2 therapy alone and not need any chemotherapy. “Or we might have patients who need a little bit of chemotherapy, maybe just one chemotherapy drug with HER2 therapy. Then there are the patients where we’re quite concerned about them and who, based on what we’re finding, need the most aggressive approach—usually combination chemotherapy with the HER2 therapy. As of now, sometimes we recommend the strongest treatment for everyone, but we know in our heart of hearts that not everyone needs that aggressive approach, which is linked to side effects and other issues,” she noted.

Both of her overriding goals inspire Connolly “…to get a strong research program off the ground here, in my new location, building on the experience that I’ve had at Johns Hopkins. I’ve learned who I need to interact with to be successful. I need to find the best scientists, the best biostatisticians, and the best partners in industry to develop new trials here with new drugs, new biomarkers,” she said.

Making life better for cancer patients is at the heart of everything Connolly does professionally. In fact, she has recently received funding for work in the area of cancer survivorship in collaboration with colleagues at the UCC School of Nursing and patient advocates.

“It’s really quite separate to what I’ve been talking about, but we know that women who go through treatment potentially will have side effects after that treatment is finished. They may have issues with their quality of life, fear of recurrence, anxiety or mood issues. The question is, once all the treatments are done and we’ve sent the patient off for intermittent follow-up, how do we best support them?

“We know they do suffer, but sometimes the patients don’t know that other people are suffering, too, and they don’t know to ask for help. Some of this relates to ongoing treatments that we recommend, such as endocrine therapies like tamoxifen or the aromatase inhibitors. Women can get significant side effects from them that impact their day-to-day quality of life.”

Connolly and her team will use this funding to set up a new Women’s Cancer Survivorship Clinic in Cork. “Many centers around the world have these important clinics established, but this will be one of the first in Ireland,” she said.

“Our hope is that we can identify the problems that women are experiencing after treatment and see if we can intervene, through this clinic structure, with appropriate referrals to specialists who can help with different symptoms, or even just educate women about handling their symptoms. Can we improve on those symptoms over time? Can we improve the quality of life of patients? My feeling is that we will, purely by listening to women and giving them an opportunity to manage how they’re feeling. We can have new drugs and new tests, but if the patients who’ve gone through all that are feeling miserable, then you’re not really doing a good job,” Connolly said, thoughtfully. “So I think examining survivorship is important. I’m feeling very hopeful that we can improve the patient experience.”

Valerie Neff Newitt is a contributing writer.