Comparison of three similar frontline breast cancer drugs reveals important differences

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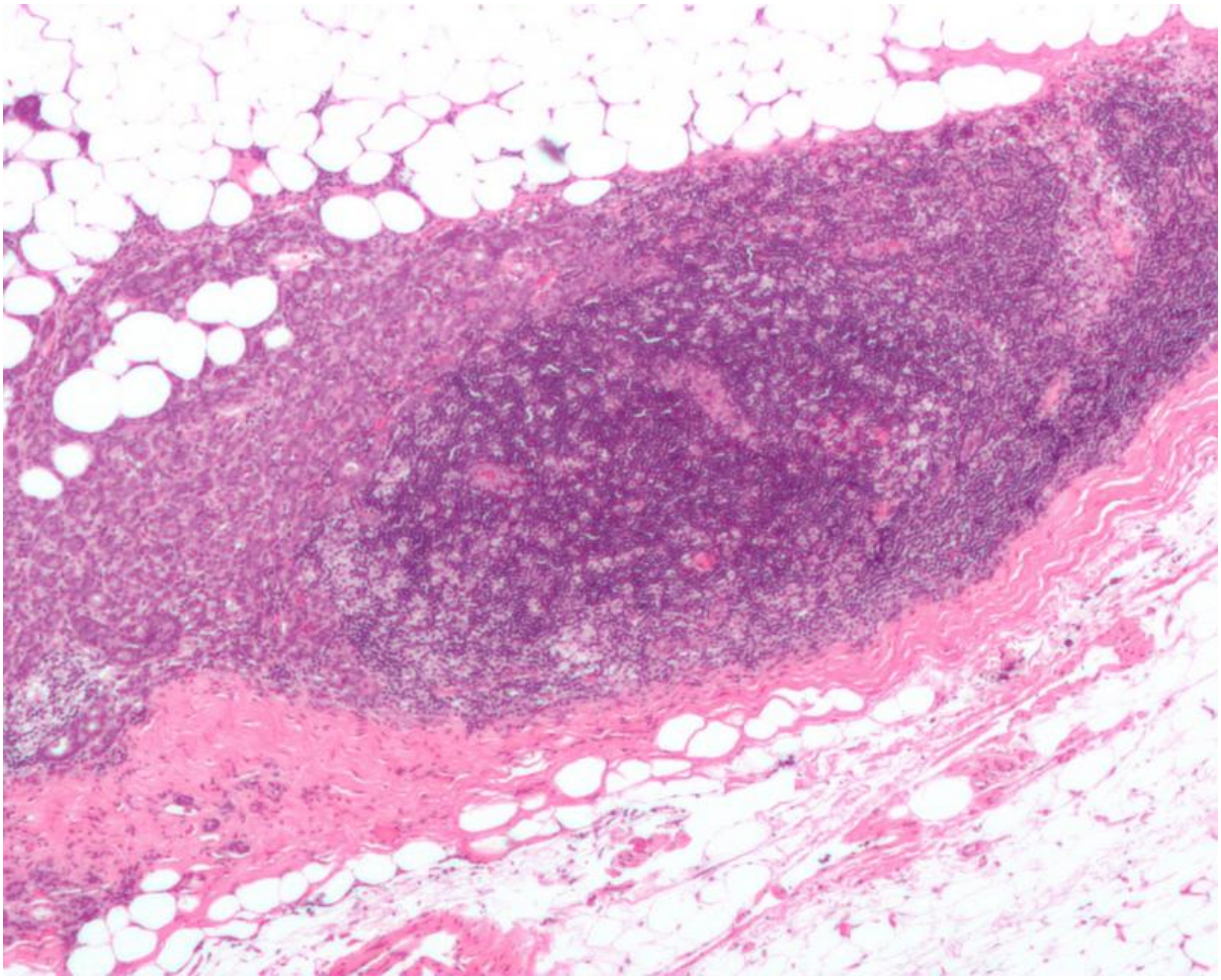

Micrograph showing a lymph node invaded by ductal breast carcinoma, with extension of the tumour beyond the lymph node. Credit: Nephron/Wikipedia

Every year, more than 250,000 women in the U.S. are diagnosed with breast cancer. When detected early, patients with the most common form—which tests positive for hormone receptors (HR+) and negative for the HER2 receptor—usually respond well to treatment. But for those in advanced stages, few treatment options existed until the recent emergence of a new class of drugs known as CDK4/6 inhibitors.

These inhibitors showed remarkable efficacy in blocking tumor growth, halting disease progression and boosting survival, leading the FDA to fast-track the approval of three such drugs to date. Today, they are used as frontline medications for patients with advanced, HR+/HER2- breast cancers. While these drugs have the same biological targets and are often used interchangeably, a growing body of evidence suggests they have important underlying differences.

Now, Harvard Medical School researchers based in the Laboratory of Systems Pharmacology at the Blavatnik Institute and the Massachusetts General Hospital have carried out the first head-to-head comparison of the three currently approved CDK4/6 inhibitors in breast cancer cell lines and animals.

Their findings, published Aug. 15 in *Cell Chemical Biology*, reveal significant and thus far poorly understood differences in biological activity among members of a drug class designated as breakthrough therapies by the FDA. One inhibitor in particular—abemaciclib—exhibited unique and potentially advantageous therapeutic activity that could help inform the design of better treatment strategies, including optimized combination therapies and circumventing drug resistance, the authors said.

"Despite the sophistication of industrial drug discovery, the activities of many drugs are not fully understood at the time of their approval by the FDA," said senior study author Peter Sorger, the HMS Otto Krayer

Professor of Systems Pharmacology in the HMS Department of Systems Biology and director of the Laboratory of Systems Pharmacology. "In this case, it appears that the drug abemaciclib may unexpectedly work in patients who are not responsive to other drugs in the class."

In their study, Sorger and colleagues, spearheaded by co-first authors Marc Hafner and Termeer Fellow Caitlin Mills, partnered with investigators based at the Termeer Center for Targeted Therapies at Mass General to form a cross-disciplinary team with the basic science and clinical expertise needed to comprehensively compare the drugs.

"Characterizing the exact target inhibition profile and the biological effects of these therapeutic agents is essential, because in some instances these differences may explain why one works and why another doesn't," said study co-senior author Dejan Juric, director of the Termeer Center. "Thorough and carefully designed studies are the only way to understand how best to sequence or combine these transformative drugs, and to identify which will be most beneficial for any individual patient."

Breakthrough family

Cells rely on a family of proteins known as CDKs (cyclin-dependent kinases) to control the complex process of cell division. These proteins are often dysfunctional in cancer cells, fueling aberrant division and uncontrolled cell growth. Early attempts to block CDK activity in tumors resulted in unsuccessful clinical trials as first-generation inhibitors affected a broad range of CDK proteins, causing the indiscriminate death of both normal and cancerous cells.

In 2015, the FDA approved palbociclib, a promising drug designed to target exclusively the CDK4 and CDK6 proteins. This high specificity led to dramatic improvements in halting tumor growth and extending progression-free survival with reduced toxicity. Two other CDK4/6

inhibitors, abemaciclib and ribociclib, were approved shortly after, all for patients with advanced HR+/HER2- breast cancer.

Although approved for the same clinical indications, these drugs differ in their chemical structures. Despite reports of different side effects in patients, it remained unclear whether they were indeed functionally equivalent.

To investigate, Sorger, Juric and colleagues applied a series of powerful experimental approaches. Over the course of several years, the team profiled the molecular activity of each of the three CDK4/6 inhibitors across a wide range of doses and dosage timings in cell lines and animal models. They analyzed the effects of these drugs on cellular growth rate, viability, gene expression and protein activity, among other indicators.

Sweet spot

Tests on a panel of 35 different breast cancer cell lines revealed a key difference in the drugs' biological activity. As expected for CDK4/6-specific inhibitors, all three agents stopped the growth of cells, the analyses showed.

At higher doses, however, only abemaciclib caused significant cancer cell death, suggesting the drug may be affecting proteins other than only CDK4/6. Palbociclib and ribociclib had minimal effects on cell death even when administered at higher doses.

Further analyses confirmed that abemaciclib has a unique profile. The drug most potently inhibited CDK4/6, and at high dosages, it also affected the activity of other proteins, acting in some ways as a pan-CDK inhibitor. Tests in mice transplanted with human breast cancer tumors affirmed these observations.

In additional experiments, the researchers developed breast cancer lines resistant to the drug palbociclib, a common occurrence that also affects patients in the clinic. These cell lines were unaffected by ribociclib, with cells continuing to grow and proliferate, but did respond to treatment with abemaciclib. Cells engineered to be unaffected by CDK4/6 inhibition also responded to abemaciclib, but not the other two drugs—further evidence of abemaciclib's pan-CDK activity.

"Whether by accident or design, abemaciclib appears to have hit a sweet spot where it is more efficacious in some regards than the other CDK4/6 inhibitors, but potentially less toxic than earlier pan-CDK inhibitors," said study co-author Kartik Subramanian, HMS postdoctoral fellow in the Laboratory of Systems Pharmacology.

Based on these results, the authors suggest that abemaciclib may have additional therapeutic benefits for a subset of tumors that remain unresponsive to treatment or have grown resistant to other CDK4/6 inhibitors. They cite a case study in which a patient's metastatic tumor reappeared after she developed resistance to palbociclib. She was switched onto abemaciclib, resulting in a notable decrease in tumor size, and continued to be successfully treated with the drug.

However, the authors caution that their study was based on preclinical, laboratory-based experiments and their findings do not present conclusions that should be used for decision-making in the clinic at this time. Rather, their data lay the necessary foundation for the design of clinical studies that can carefully and thoroughly assess which strategies for CDK4/6 inhibitor treatment would be of greatest benefit to patients.

Importantly, the same head-to-head comparison approach to profile similar drugs could be applied to other classes of drugs, the authors said.

"Our findings are an important reminder that just because drugs are

marketed to have the same nominal targets, it doesn't mean they are necessarily equally effective in all situations," Mills said. "The most common form of breast cancer is hormone receptor positive, and for CDK4/6 inhibitors, there is the potential to make an enormous difference for a very large number of women by understanding how these drugs could be optimally used."

"The study also highlights the complex and often surprising ways, in which independent but complementary research by scientists in industry and academia can advance precision medicine," Sorger said.

More information: Marc Hafner et al, Multiomics Profiling Establishes the Polypharmacology of FDA-Approved CDK4/6 Inhibitors and the Potential for Differential Clinical Activity, *Cell Chemical Biology* (2019). DOI: 10.1016/j.chembiol.2019.05.005

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