MedicalXpress

Side effects not a major problem for new class of breast cancer drugs

July 13 2017

A ground-breaking new class of oral drugs for treating breast cancer, known as cyclin-dependent kinase (CDK) inhibitors, are generally well-tolerated, with a manageable toxicity profile for most patients. This is the conclusion of a comprehensive review of toxicities and drug interactions related to this class of drugs, recently published in *The Oncologist*.

The excitement surrounding CDK inhibitors is due to their great potential for treating the most common type of breast cancer known as hormone receptor-positive (HR+) metastatic breast cancer, in which the cancer cells express hormone receptors. The first CDK inhibitors were recently approved by the US Food and Drug Administration (FDA), with palbociclib (Ibrance) approved in February 2015 and ribociclib (Kisqali) approved in March 2017, while a third, abemaciclib, is currently undergoing Phase 3 trials. All three CDK inhibitors have been designated "breakthrough therapies" by the FDA.

"CDK inhibitors have changed the landscape of management of HR+ breast cancer," says Aditya Bardia, a specialist in breast cancer at the Massachusetts General Hospital Cancer Center in Boston, US, and the senior and corresponding author on the article.

A major hallmark of cancer cells is their ability to multiply rapidly; CDK inhibitors interfere with this process by blocking the activity of enzymes known as CDKs, particularly CDK 4 and CDK 6, that help to regulate cell division. For effectively treating breast cancer, CDK

inhibitors are usually combined with endocrine therapy, which works by preventing hormones from binding with their respective receptors on the cancer cells.

"Given the excitement with these drugs, there has been considerable uptake in clinical practice for management of patients with metastatic breast cancer," explains Bardia. "However, these agents are different from endocrine therapies, and have a unique set of side effects. Therefore, we felt it was important to have a dedicated review article on clinical management of potential toxicities and drug interactions seen with the use of CDK 4/6 inhibitors and summarize practical management strategies for a medical oncologist."

Bardia and his team reviewed all the publicly available studies conducted on palbociclib, ribociclib and abemaciclib, most of which had formed part of the approval process for these drugs. For palbociclib and ribociclib, the most common side effect was a low level of white blood cells, a condition known as neutropenia, which can increase the chance of infection. This makes sense, because CDK inhibitors are known to affect the division of blood cells in the bone marrow, including white blood cells. However, since the impact on white blood cells is temporary and dose-dependent, the counts usually return to normal with dose-interruption or dose-reduction of palbociclib or ribociclib.

While all the CDK 4/6 inhibitors affect the cell-cycle, there are slight differences between them. For example, neutropenia appears to be less common with abemaciclib; other side effects such as diarrhea and fatigue appear to be more common. Various other, less common side effects are sometimes also seen with CDK 4/6 inhibitors, including nausea and alopecia, but they're usually mild and can often be treated by reducing the dose and taking regular breaks.

Bardia and his team cautioned that patients and treating physicians

should be aware of certain drug-drug interactions with CDK 4/6 inhibitors, particularly for substances that inhibit the activity of an enzyme known as CYP3A, such as the antibiotic clarithromycin and grape juice. This is because CYP3A is the prime enzyme responsible for breaking down CDK 4/6 inhibitors in the liver, and thus inhibiting its activity could lead to the build-up of high levels of the drug.

CDK 4/6 inhibitors are now being investigated for their ability to treat various other cancers, including lung cancer, prostate cancer and ovarian cancer, so their efficacy and excellent safety profile could eventually prove to have benefit in diseases besides breast cancer.

"Ongoing trials are exploring the role of CDK 4/6 inhibitors in the adjuvant setting, so the use of these drugs is likely to expand significantly in the near future," commented Gabriel Hortobágyi at MD Anderson Cancer Center in Houston, TX, who is a section editor of *The Oncologist* and was not involved in the review. "The article by Spring et al summarizes the published toxicity data of the three leading CDK 4/6 inhibitors and provides clear, practical guidelines for managing the more common side effects and toxicities. Bringing together this information into one objective manuscript is a good service to the community."

More information: Clinical Management of Potential Toxicities and Drug Interactions Related to CDK 4/6 Inhibitors in Breast Cancer: Practical Considerations and Recommendations. Laura M. Spring, Mark Zangardi, Beverly Moy, Aditya Bardia. *The Oncologist*. Published Online: July 17, 2017; DOI: 10.1634/theoncologist.2017-0142