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Significance of Renal Function Monitoring During Treatment with Abemaciclib

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About the Study

Treatment strategies for hormone receptor-positive (HR+), human epidermal growth factor receptor 2-negative (HER2-) advanced breast cancer have changed in recent years. Cyclin-dependent kinase 4/6 (CDK4/6) inhibitors are novel agents that directly block the activity of the cyclin D-CDK4/6 holoenzyme and prevent cell cycle progression from G1 to S phase by preventing the phosphorylation of retinoblastoma protein, which sequesters E2F family of transcription factors [1,2]. Among the various breast cancer subtypes, estrogen receptor-positive (ER+) breast cancer is the most sensitive to growth inhibition.

Randomized phase III studies in patients with HR+/HER2- breast cancer confirmed that the addition of CDK4/6 inhibitors to endocrine therapy significantly improved progression-free survival (PFS) compared with endocrine therapy alone in those with metastasis [3-7]. The US Food and Drug Administration has approved palbociclib, ribociclib, and abemaciclibin combination with specific endocrine therapies for the treatment of HR+/HER2- metastatic breast cancer. Palbociclib and abemaciclib have been approved in Japan for the treatment of HR+/HER2- metastatic breast cancer. Abemaciclib is the most recently approved CDK4/6 inhibitor in Japan.

The adverse event profile is slightly different between palbociclib and abemaciclib. The most common adverse events associated with palbociclib treatment are neutropenia, leukopenia, fatigue, nausea, arthralgia, and alopecia whereas the most common adverse events in patients treated with abemaciclib are diarrhea, neutropenia, nausea, and fatigue. In addition to neutropenia, anemia and thrombocytopenia are also known as CDK 4/6 inhibitors specific side effects. AST and/or ALT increased which is not as common as hematological toxicity with CDK4/6 inhibitors is reported more in patients treated with abemaciclib than in patients treated with palbociclib. Additionally, approximately 25% patients treated with abemaciclib are reported to exhibit increased serum creatinine levels whereas to date none of the clinical trials on palbociclib have reported increased serum creatinine levels [3-5,7].

In our institute, the safety profile of abemaciclib administered in combination with endocrine therapy is generally consistent with that reported in previous studies [5,8,9]. However, the proportion of patients with elevated serum creatinine levels, reaching up to 68%, is higher than that reported previously, most of which involved low-grade increases in serum creatinine. This difference might be explained by the design of the clinical trials, in which safety was not a primary endpoint, and some laboratory abnormalities might have been missed. Studies have proposed that serum creatinine might not accurately reflect renal function in patients receiving abemaciclib since it inhibits renal transporters that mediate tubular secretion of creatinine [5,10]. A post hoc analysis of the MONARCH 1 study demonstrated that the rise in serum creatinine was not associated with elevation in cystatin C and that cystatin C-calculated glomerular filtration rate (GFR) was not reduced; thus, the rise in serum creatinine was not temporally associated with reduced renal function [10-12]. However, the underlying mechanism and the extent of continuous alterations in serum creatinine induced by abemaciclib affects renal function remain unclear. The MONARCH 3 study demonstrated that the median PFS in the abemaciclib arm was 28.18 months [5]; thus, it might be challenging to tolerate an increase in creatinine induced by abemaciclib, even one that is low-grade and is not associated with direct renal injury, over an extended time period, Therefore, cystatin C and GFR should be monitored during treatment with abemaciclib especially in patients with increased serum creatinine levels to recognize signs of reduced renal function.

In conclusion, the availability of CDK 4/6 inhibitors has dramatically changed the treatment paradigms for HR+/HER2- metastatic breast cancer. However, these novel agents have specific adverse events profiles. The most common adverse event with abemaciclib is diarrhea, whereas increased serum creatinine is uncommon and tend to be overlooked compared with diarrhea. Although a temporal elevation in serum creatinine may not have a direct effect on renal function, long-lasting creatinine abnormalities may be associated with renal dysfunction. Thus, periodical assessment of cystatin C and GFR may be useful to detect signs of renal dysfunction during abemaciclib treatment.

Conflict of Interest

The authors have no conflicts of interest to declare.

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