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Abemaciclib-induced lung damage leading to discontinuation in brain metastases from breast cancer: A Case report

Abemaciclib discontinuation due to lung damage

Hiroyasu Yamashiro, Nao Morii

Abstract

BACKGROUND

This case report addresses the dearth of effective therapeutic interventions for central nervous system metastases in patients with HER2-negative breast cancer. It presents a unique case of a woman with estrogen receptor (ER)-positive, HER2-negative breast cancer who developed brain metastasis. The report highlights her initial favorable response to abemaciclib and letrozole therapy but necessitated discontinuation due to drug-induced lung damage (DILD).

CASE SUMMARY

In this comprehensive case summary, we present the clinical journey of a woman in her 60s, who 11 years following primary breast cancer surgery, was diagnosed with multiple brain metastases. As a third-line systemic therapy, she underwent treatment with abemaciclib and letrozole. This treatment approach yielded a near-partial response in her metastatic brain lesions. However, abemaciclib administration had to be prematurely halted due to the emergence of DILD, as confirmed by computed tomography scan. The DILD improved after 1 mo of cessation. Despite ongoing

therapeutic efforts, the patient's condition progressively deteriorated, ultimately resulting in death due to progression of the brain metastases.

CONCLUSION

This case underscores the challenge of managing adverse events in responsive brain metastasis patients, given the scarcity of therapeutic options.

Key Words: Breast cancer; HER2 negative; Brain metastasis; Abemaciclib; Drug-induced interstitial lung damage; Case report

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Core Tip: In this case report, we address the critical issue of limited therapeutic options for HER2-negative breast cancer patients with brain metastases. We present a compelling case of a woman with ER-positive, HER2-negative breast cancer who exhibited an encouraging response to abemaciclib and letrozole therapy for brain metastases. However, this treatment had to be discontinued due to drug-induced lung damage (DILD). This report emphasizes the challenging balance between efficacy and adverse events in managing brain metastases and highlights the pressing need for alternative treatment strategies in this patient population.

INTRODUCTION

Central nervous system (CNS) metastasis in primary breast cancer occurs in 10–15% of advanced/recurrent breast cancer cases[1]. However, drug therapy for brain metastases of cancer has been considered less effective due to the presence of the brain-blood barrier (BBB), which restricts the entry of many drugs into the CNS. In certain phenotypes such as HER2-positive breast cancer, treatment outcomes of CNS metastasis have been improving with the development of new drugs[2]. However, currently no

drug has significant efficacy in treating CNS metastasis from HER2 negative breast cancer, and radiation therapy remains the first choice.

Two cyclin-dependent kinase (CDK) 4/6 inhibitors, abemaciclib and palbociclib, are available as insurance-covered treatment in Japan. These drugs, when combined with hormonal therapy, were effective in prolonging progression-free interval (PFI) in ER-positive/HER2-negative metastatic/recurrent breast cancer to twice that achieved previously with hormonal therapy alone[3]. Abemaciclib can cross the BBB[4], and it is expected to be effective against brain metastasis of ER-positive/HER2-negative breast cancer.

Here, we report a case of brain metastasis of ER-positive/HER2-negative primary breast cancer that initially responded to concomitant therapy of abemaciclib and letrozole but required termination owing to drug-induced lung damage (DILD).

CASE PRESENTATION

Chief complaints

A postmenopausal woman in her 60s revisited our hospital complaining of unsteadiness or dizziness.

History of present illness

Several months ago, the patient became aware of dizziness and the symptoms gradually worsened. She was not aware of nausea, paralysis, muscle weakness, or memory loss.

History of past illness

She underwent mastectomy and axillary lymph node dissection for breast cancer 11 years ago. The pathological diagnosis was mucinous carcinoma, histological grade 2, pT1c, n0(0/7), ER-positive, progesterone receptor-positive, and HER2-negative (score 0). For 5 years after surgery, she received endocrine therapy and was no longer followed up after being recurrence-free for 10 years postoperatively.

Personal and family history

She had no particular personal and family medical history.

Physical examination

On physical examination no notable abnormalities were observed.

Laboratory examinations

The laboratory examination results were unremarkable.

Imaging examinations

Head magnetic resonance imaging (MRI) indicated multiple brain metastases (Figure 1); no trunk lesions were observed on computed tomography (CT).

LABORATORY EXAMINATIONS

The laboratory examination results were unremarkable.

PHYSICAL EXAMINATION

On physical examination no notable abnormalities were observed.

FINAL DIAGNOSIS

Late (more than 10 years after primary radical surgery) recurrence of breast cancer. Multiple brain metastases.

TREATMENT

After whole brain irradiation (40 Gy/20 Fr), exemestane treatment was initiated. Although the brain metastases showed partial response (PR), in the 12th year postoperatively, lymph node and adrenal metastases were detected by CT. Consequently, the treatment was changed to palbociclib plus letrozole. Thereafter, owing to deterioration of the pre-existing cerebellar metastasis, localized irradiation was performed. In the 13th year postoperatively, the brain metastases progressed

(Figure 2A), so treatment was changed to abemaciclib plus letrozole as the third-line treatment. Three months later, MRI showed attenuation of the brain metastases and the contrast effect (Figure 2B), almost reaching a PR. However, DILD was noted on CT (Figure 3), which necessitated the termination of abemaciclib. No other grade 3 or higher hematological toxicity, diarrhea, or fatigue occurred, and these could be managed with appropriate dose reduction.

OUTCOME AND FOLLOW-UP

The DILD improved after 1 mo of cessation. The patient continued treatments with TS-1 and fulvestrant but died in the 14th year postoperatively due to progression of the brain metastases.

DISCUSSION

We experienced a case in which abemaciclib was successful for brain metastasis of ER-positive/HER2-negative breast cancer but had to be discontinued due to DILD. Brain metastasis is reported to occur in 10–15% of cases of advanced or recurrent breast cancer[1], and the mean survival after the appearance of brain metastasis varies depending on the subtype, from several years for HER2-positive breast cancer to less than 6 mo for triple-negative (HER2, ER, and progesterone receptor all negative) breast cancer[5-7].

Breast cancer is recognized as a solid tumor that often responds well to pharmacotherapy, and advancements in translational research have significantly expanded the array of available drugs. However, conventional drugs are limited in their effectiveness for brain metastases of breast cancer because of the BBB and low cerebrospinal fluid penetration[8].

Some case reports and Phase II trials have indicated a[9] response rate of 5.2% to abemaciclib in brain metastases of ER-positive breast cancer and the overall outcomes have been less than satisfactory. Capivasertib (an AKT inhibitor) and alpelisib (a PI3K

inhibitor) may have some potential for brain metastasis of hormone receptor-positive breast cancer.

Trastuzumab-deruxtecan (T-DXd) is an antibody-drug conjugate that covalently binds trastuzumab, a humanized monoclonal antibody, with deruxtecan, a topoisomerase I inhibitor (a derivative of exatecan). T-DXd has shown promising results with a high response rate of 47.1% for brain metastases of HER2-positive breast cancer[10] owing to its unique mechanism of action. With HER2-low (HER2 score of 1 or 2 and FISH-negative) recurrent metastatic breast cancer being added as an indication, T-DXd is expected to show effectiveness in brain metastases of breast cancer previously considered as ER-positive or triple-negative with low HER2 expression[11]. The first-line drug for ER-positive/HER2-negative metastatic/recurrent breast cancer is a CDK4/6 inhibitor, but if accompanied by brain metastases, T-Dxd may be a better first-line choice.

In global trials of abemaciclib (MONARCH 2, 3, and E)[12-14], DILD was reported in approximately 2–3% of cases. Although DILD is not often fatal if appropriate monitoring and early intervention occur, in cases of grade 2 or higher severity, treatment must often be terminated without the possibility of it being resumed. Underlying lung diseases such as interstitial pneumonia can be risk factors for DILD, but the exact mechanism of onset is not fully understood, and preventive measures have not been established. CDK4/6 inhibitors, abemaciclib, and palbociclib can be prescribed under Japanese insurance; however, palbociclib has a high incidence of hematological toxicity, particularly neutropenia, reported at 78% (66% grade 3) in a Phase III[3] study. Abemaciclib also has hematological toxicity[12-14] but is clinically characterized by non-hematological toxicity, particularly diarrhea and fatigue.

As this is a case report, our findings are yet unvalidated. However, they may provide an opportunity to consider the importance of limiting treatment termination due to adverse events. This is because currently no drugs have shown a dramatic effect on brain metastases of breast cancer.

CONCLUSION

We present the case of a patient with brain metastases from primary breast cancer in whom abemaciclib had to be terminated owing to DILD. While we anticipate the development of drugs that are effective for brain metastases, exploring strategies to minimize treatment terminations due to toxicities remains an important approach.

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