Case Report

Palbociclib Associated Deep Vein Thrombosis: A Case Report

Palbociclib Ilişkili Derin Ven Trombozu: Olgu Sunumu

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ABSTRACT

Cyclin-D-cyclin dependent kinase 4/6 (CDK 4/6) inhibitors started a new era in metastatic hormone receptor positive breast cancer. Ribociclib, palbociclib and abemaciclib (CDK 4/6 inhibitors) are used in combination with endocrine therapy and they provide a significant benefit in progression free and overall survival. Fatigue, neutropenia, anemia, and diarrhea are commonly seen side effects which are easily manageable with dose modifications. Herein, we presented a case of deep vein thrombosis developed twice under palbociclib treatment which is a rarely reported side effect causing cessation of the treatment.

Keywords: CDK4/6 inhibitors, metastasis, thrombosis

ÖZET

Siklin-D-sikline bağımlı kinaz 4/6 (CDK 4/6) inhibitörleri metastatik hormon reseptörü pozitif meme kanserinde yeni bir dönem başlatmıştır. Ribociclib, palbociclib ve abemaciclib (CDK 4/6 inhibitörleri) endokrin tedavisi ile kombinasyon halinde kullanılır ve progresyonsuz ve genel sağkalımda önemli bir fayda sağlamıştır. Yorgunluk, nötropeni, anemi ve diyare yaygın görülen ve doz modifikasyonları ile kolaylıkla kontrol edilebilen yan etkilerdir. Burada, palbosiklib tedavisi altında gelişen, tekrarlayıcı ve tedavinin kesilmesi ile sonuçlanan nadir bir yan etki olan derin ven trombozu olgusunu sunduk.

Anahtar Kelimeler: CDK 4/6 inhibitörleri, metastaz, tromboz

Introduction

Cyclin proteins constitute the control step of the mitosis in the cell cycle. It is known that cyclin-D-cyclin dependent kinase 4/6 (CDK 4/6), one of these proteins, is responsible for the resistance to hormonal therapies in hormone receptor positive breast cancer and can cause excessive proliferation in cancer cells as a result of increased activity. CDK4/6 inhibitors (CDKIs) act by suppressing this protein. The estrogen pathway in breast cancer also escapes from the CDK4/6 control step and causes tumor growth[1]. Therefore, it has been suggested that inhibition of the estrogen and CDK4/6 pathways together may be an effective treatment method in terms of both preventing the development of hormonotherapy resistance and delaying tumor growth. Today, the use of CDKIs in the first step with hormonotherapy in hormone receptor positive metastatic breast cancer, is a standard care of treatment. The most common side effects of CDKIs are fatigue, alopecia, nausea, diarrhea, neutropenia and anemia[2]. Herein, we presented a breast cancer case who developed thromboembolism under palbociclib treatment which is a rarely reported side effect causing discontinuation of the treatment in the literature.

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Case report

A 73-year-old female patient referred to our oncology clinic in May 2020, after diagnosed with breast cancer. She noticed a lump in her right breast 4 months ago. The mammogram and breast ultrasonography revealed 32x29x38mm mass lesion with micro-calcifications in her right breast causing distortion (BIRADS 5) and 14mm pathological right axillary lymph node. A positron emission tomography (PET) scan done with preliminary diagnosis of breast cancer showed 18-F FDG uptake at the right breast upper quadrant (3x2.5cm) and axillary lymph node (18mm). The lesions in right lung, liver and on 2nd rib were interpreted as metastases. Cranial magnetic resonance imaging did not reveal any pathology. She underwent a tru-cut breast biopsy. The pathological examination of the biopsy specimen showed invasive breast carcinoma. The immunohistochemical examination findings were as followed; estrogen receptor (ER) 100%, progesterone receptor (PR) 30%, Ki67 15%, c-erb-B2 score 0. Patient's medical history revealed hyperthyroidism and hypertension. On physical examination, patient's Eastern Cooperative Oncology Group (ECOG) Performance Status score was 1 and 3x4cm ulcerated breast mass was present on the right side. Patient had stage IV breast cancer. Since her hemotological and biochemical labarotory parameters were in normal ranges, palbociclib 125mg and letrozole 2.5mg were administered. The patient's neutrophil count was $4.85x10^3$/L on her 15th day control. One month later, the laboratory results were as followed; white blood cell: $4.41x10^3$/L, neutrophil: $1.48x10^3$/L, hemoglobin: 12.7g/dL, platelet: $134x10^3$/L. Although the neutropenia was grade 2, taking the patient's age into consideration as well as grade 3 fatigue, dose modification was planned to 100mg before second cycle. In the third month of treatment, the patient complained of right leg pain. The venous ultrasound showed deep vein thrombosis so low molecular weight heparin and rivoraxaban were prescribed. Her neutrophil level was $8.36x10^3$/L. We continued palbociclib and letrozol. After one month, while on anticoagulation treatment, blood clots developed in the left leg. She had operation and endovascular stent was placed. She was consulted with hematology. Since she had cancer, does not have a history of thromboembolic event as well as family history, hematology department found it inappropriate to test for genetic thrombophilia. After her second thrombosis, we decided to stop palbociclib treatment and continue with letrozole. The patient is under hormone replacement and anticoagulant treatment for 6 months without new thromboembolic event.

Discussion

Breast cancer is the most common type of cancer in women worldwide, and 60-75% of the cases are ER+[3]. In recent years, CDKIs have been shown to play a role in mediating the resistance to endocrine therapy. Abemaciclib, ribociclib and palbociclib are CDKIs that are approved by Food and Drug Agency (FDA).

PALOMA-2 trial demonstrated improved progression free survival (PFS) in palbociclib and letrozole arm compared with letrozole and placebo[4]. After a median follow-up of approximately 38 months, median PFS was 27.6 months. Although the efficacy is proven, the risk of venous thromboembolism (VTE) with this treatment, which is one of the major mortality and morbidity reasons in breast cancer patients, had never been reported. Thein et al. undertook a systematic review and meta-analysis of randomized controlled trials to determine the risk of VTE with abemaciclib based regimens versus other CDKI containing regimens[5]. No significant increase in the risk of VTE was noted with palbociclib in this meta-analysis. On the other hand, Gervaso et al. conducted a retrospective cohort study of

consecutive metastatic breast cancer patients who received any of CDKIs[6]. They included 424 patients where palbociclib was the most commonly used CDKI (91.8%). Venous thromboembolism occurred in 38 patients (6.3%) at 1 year, where deep vein thrombosis (DVT) was seen in 52.6%. But, they didn't differentiate the patients who were on palbociclib and had DVT. Watson et al., however, found the VTE rate around 11% in 66 patients receiving palbociclib[7]. In a recent analysis including 266 patients with 89% using palbociclib, the 1-year incidence of thrombosis was 10.9% for palbociclib, 8.3% for ribociclib and 4.8% for abemaciclib [8]. DVT was the most frequent thrombotic event.

VTE is seen in 1 to 2 out of 100 women as a side effect of aromatase inhibitors and they are even the preferred hormonotherapy agents when the patient has a history of inherited thrombotic disorder[8,9]. In our case, since the patient is elderly and does not have a history of tromboembolic event, we excluded the probability of genetic disorders. Palbociclib was the reason of thrombosis in our case. The fact that the patient had a second attack, especially on anticoagulation therapy, and stabilized after discontinuation of the drug is another entity that points palbociclib as the responsible factor.

Although the regulatory agencies such as the FDA and European Medicines Agency do not currently provide any warning for thromboembolic complications during palbociclib therapy, considering the meta analysis and case reports, physicians should be alert for the development of venous thromboembolism during the treatment with CDKIs. However, more studies are needed including larger number of breast cancer patients receiving CDKIs.

Consent: Informed consent is given by the patient.

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