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Challenges of oral antithrombotic therapy in breast cancer patients treated with cyclin-dependent kinase inhibitors: A case report

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Abstract

Breast cancer patients treated with cyclin-dependent kinase inhibitors may need concomitant antithrombotic drugs for therapy and prevention purposes. Optimal management of drug-drug interactions is necessary in this setting. We describe the case of a patient who developed a cerebrovascular event during the treatment with palbociclib. Consultation to guidelines and interdisciplinary involvement was used to avoid dangerous interactions with direct oral anticoagulants and statins.

Abbreviations: AUC: Area Under the Curve; Cmax: Maximal (peak) plasmatic concentration; CT: Computed tomography; CYP: Cytochrome P450; FDA: US Food and Drug Administration.

Introduction

Palbociclib, ribociclib and abemaciclib are third generation cyclin-dependent kinase 4 and 6 inhibitors approved and widely used for the treatment of breast cancer with positive hormone receptors in combination with hormone therapy [1]. A substantial part of candidate patients for treatment with these drugs are elderly, and some of them have comorbidities or other factors that increase the risk of thromboembolic events. Systematic reviews and meta-analyses show an increased risk of thromboembolic events, including pulmonary embolisms [2] and venous thromboembolisms [3] in patients who received treatment with cyclin-dependent kinase inhibitors. This risk has been also described in studies of real-world practice [4]. There are multiple potential pharmacokinetic interactions between cyclin-dependent kinase inhibitors and several drugs used in the prevention and treatment of thromboembolic and cardiovascular events, including some anticoagulants, platelet inhibitors and lipid-lowering compounds [5].

We describe the case of a patient with metastatic breast cancer on treatment with palbociclib who needed therapy for preventing embolic and thrombotic complications and was the subject of multidisciplinary consultations between different medical specialties in order to optimize her drug therapy.

Case description

A 74-year lady had a medical history of hypertension, diabetes mellitus, Parkinson disease and atrial fibrillation. She was diagnosed with breast cancer in 2003, and treated with surgery, adjuvant chemotherapy and radiotherapy. Widespread bone metastases were diagnosed in September 2020, and she was started on therapy with letrozole (2,5 mg/d) plus palbociclib (125 mg/d for 3 weeks every 4 weeks). She was on treatment with apixaban for the prevention of embolic events from her atrial fibrillation. In January 2021 a stroke code was activated as she had a sudden weakness of the left arm and leg on wakening. During admission at the Stroke Unit there was a progressive improvement towards disappearance of the neurological focality. Imaging studies with angioCT scan, perfusion CT scan and cranial magnetic resonance did not reveal acute lesions. A point-of-care doppler ultrasound (Philips CX50) showed significant carotid stenosis (Figure 1). The diagnosis was of transient ischemic attack. Revascularization was discarded, and she continued anticoagulant therapy and started high doses of atorvastatin (80 mg/d). Palbociclib was temporarily suspended because of the significant interaction with atorvastatin, but it was resumed a few weeks later when an interdisciplinary evaluation between Neurology and Medical Oncology gave priority to palbociclib over atorvastatin at that time. Apixaban was also changed to edoxaban after an interdisciplinary evaluation between Hematology and Medical Oncology. In June 2021 she continues on treatment with palbociclib and edoxaban without new thrombotic, bleeding or cardiovascular events.

Direct oral anticoagulants like apixaban are increasingly used for the prevention and treatment of thromboembolic events in patients with cancer, and potential interactions with anticancer agents is among the concerning points of some of these drugs [6]. A recent review of the FDA Adverse Event Report System regarding thromboembolic events in patients on treatment with cyclin-dependent kinase inhibitors reported that more than one hundred of such patients were taking direct oral anticoagulants but was unable to distinguish if it was before and/or

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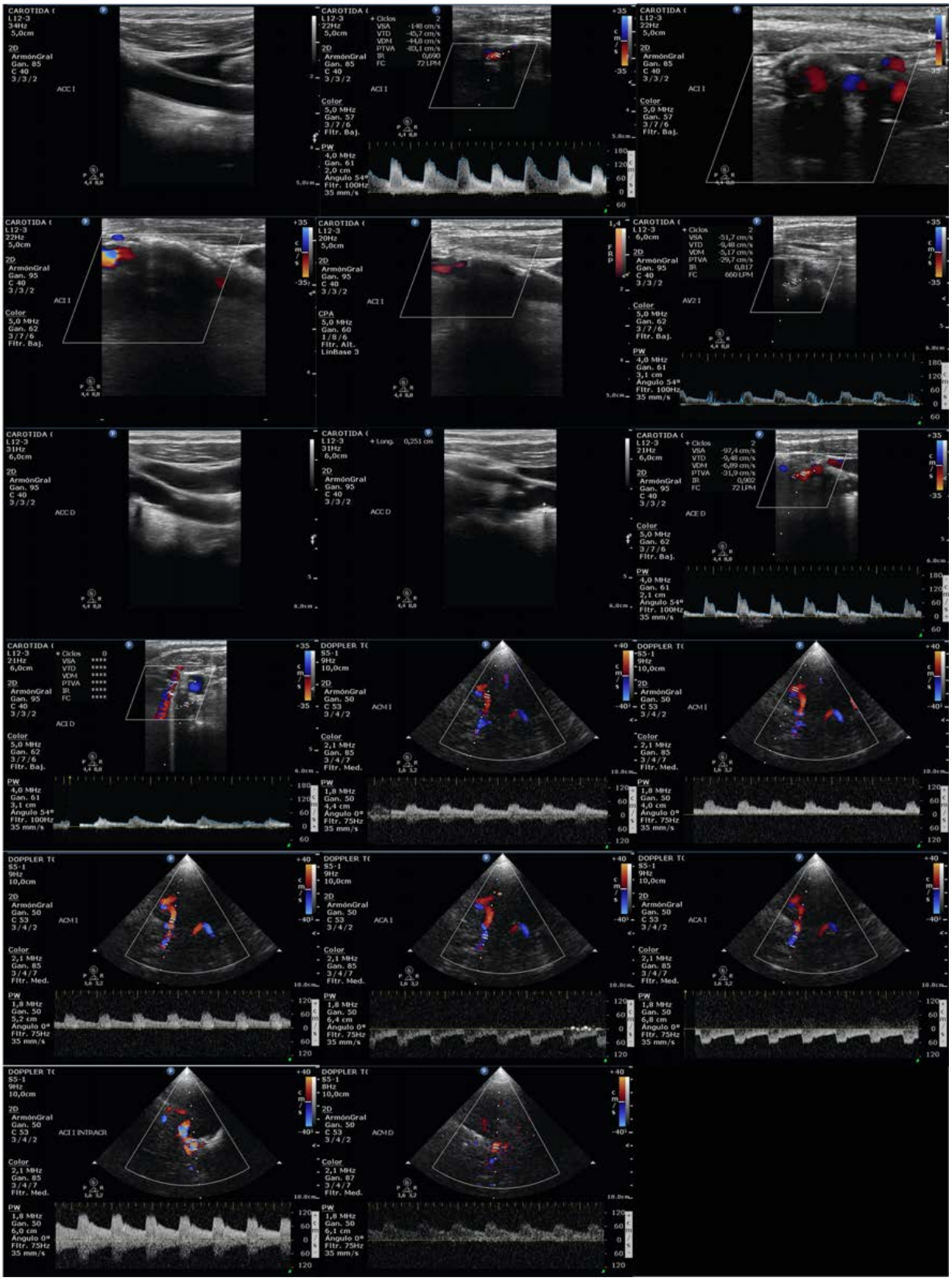

Figure 1. Point-of-care cervical and transcranial doppler ultrasound showing significant stenosis in the right and left internal carotid arteries

Table 1. Published severe adverse events (liver/muscle) with use of CDKI plus statins

Authors	CDKI	Statin	Rhabdomyolysis	Liver injury	Outcome
Gopalan, *et al.* [15]	Palbociclib	Simvastatin	Yes	Yes	Not stated
Nelson, *et al.* [16]	Palbociclib	Atorvastatin	Yes	Yes	Death
Nersesjan, *et al.* [17]	Palbociclib	Simvastatin	Yes	No	Recovery
Streicher, *et al.* [18]	Ribociclib	Simvastatin	Yes	No	Recovery
Atallah, *et al.* [19]	Palbociclib	Atorvastatin	No	Yes	Terminal

CDKI: Cyclin-dependent kinase 4 and 6 inhibitors

after the thromboembolic events [7]. 57 out of 424 patients treated with cyclin-dependent kinase inhibitors in a hospital series were already on treatment with anticoagulants (5 with direct oral anticoagulants) with none of them experiencing venous thromboembolic events [8].

Published case reports on the use of direct oral anticoagulants during the treatment with cyclin-dependent kinase inhibitors are scarce. One patient on palbociclib was started on rivaroxaban after a diagnosis of deep vein thrombosis [9]. She had no problems with the direct oral anticoagulant but developed a saddle-type pulmonary embolism two weeks later. A Consensus on the Management of Concomitant Medication in Patients on Treatment with Palbociclib or Ribociclib indicates that apixaban and rivaroxaban should be avoided in combination with such drugs [5]. Acenocoumarol, warfarin, argatroban and bivalirudin are considered safe options. Dabigatran and edoxaban display a minor statin interaction effect, and caution instead of avoidance is suggested by this consensus. A comprehensive review on the subject advices to avoid concomitant use of apixaban or rivaroxaban if ribociclib is used at 600 mg/d, and monitoring toxicity of direct oral anticoagulants when used with abemaciclib, palbociclib or a dose of 400 mg/d of ribociclib [10]. There is little information on the treatment of thromboembolic events in patients taking cyclin-dependent kinase inhibitors, but low molecular weight heparin was the most common treatment after venous thromboembolic events that developed during the treatment with abemaciclib in the pivotal MONARCH 2 and MONARCH 3 randomized trials, with no interruption of this drug or reduction in the dose [11]. As patient survival is relatively long in metastatic breast cancer patients treated with cyclin-dependent kinase inhibitors [1], some clinicians will consider to switch to direct oral anticoagulants in these patients.

The potential for interaction between cyclin-dependent kinase inhibitors and lipid-lowering statins is more frequent, since the use of these drugs is common. A real-world study from a longitudinal claims database described that more than 20% of an extensive series of patients treated with palbociclib were also on treatment with lipid-lowering agents [12]. An experimental study showed that standard doses of palbociclib during 2 months moderately increased the AUC and Cmax of atorvastatin (40 mg/d) and the metabolite atorvastatin lactone between 1.25 fold and 2-fold, with elevation in the risk of statin-induced muscular toxicity [13]. Obviously, a greater dose of atorvastatin increases the risk. The dose of atorvastatin used in our patient was 80 mg/d, according to the results of trials for reduction of vascular events [14]. Several cases of severe and sometimes fatal rhabdomyolisis and/or liver injury have been described in patients on concomitant treatment with some cyclin-dependent kinase inhibitors and atorvastatin or simvastatin [15-19, Table 1). A Consensus on the Management of Concomitant Medication in Patients on Treatment with Palbociclib or Ribociclib stated that simvastatin and atorvastatin should be avoided in patients on treatment with such drugs [5]. Pitavastatin is regarded as a safe option statin with low risk of interaction. Fluvastatin, pravastatin and rosuvastatin have a minor interaction effect with palbociclib and ribociclib and caution instead of avoidance is suggested by this consensus. A review by other authors includes abemaciclib with the same recommendations [20]. Nevertheless, there is a major difference since abemaciclib does not have a clinically meaningful effect on pharmacokinetics of CYP3A4 substrates (like statins) in patients with cancer [21]. This is recognized in the online cyclingtoool platform on pharmacokinetics and interactions of cyclin-dependent kinase inhibitors developed by the SOLTI group (www.cyclibtool.org) We must also consider that the risk of statin-related rhabdomyolysis is increased in elderly patients. The Young International Society of Geriatric Oncology gives a general recommendation to close monitoring of symptoms or dose reduction of concomitant sensitive substrates (as some statins) in patients on treatment with cyclin-dependent kinase inhibitors [22].

Conclusion

The potential interaction between cyclin-dependent kinase inhibitors and some anticoagulants and lipid-lowering agents must be considered in terms of patient safety. There have been consensus developments on this subject with practical and useful information. An interdisciplinary approach is important in order to prioritize and optimize the use of concomitant drugs in this setting.

Authorship and Contributorship

All the authors contributed equally to this manuscript.

Competing interests

JJI received honoraria from Pfizer for focus discussions.

Ethical aspects

The patient signed informed consent to participate in a study on cardiovascular complications in long-term survivors of breast cancer (ILL-CAR-2018-1) that was approved by the Ethical Committee of our region. She also gave authorization for the publication of these clinical findings.

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