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Case report

Enhanced dermatologic toxicity following concurrent treatment with palbociclib and radiation therapy: A case report

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ABSTRACT

Background: Cyclin-dependent kinase (CDK) 4/6 inhibitors represent a new class of targeted therapy options for the treatment of estrogen receptor-positive (ER+) human epidermal growth factor 2-negative (HER2-) metastatic breast cancer. There are currently no published prospective data on the safety of use of radiation treatment with palbociclib.

Case: We describe the case of a patient with metastatic breast cancer who received radiation treatment to a metastatic supraclavicular lymph node to planned 60 Gy in 30 fractions while on palbociclib, a selective inhibitor of CDK4/6. The patient developed early radiation toxicities including esophagitis and dermatitis that progressed to a severe left neck skin breakdown in the radiation field, resulting in the need for hospitalization. She had a break in treatment but was able to finish the radiation without palbociclib. Her tumor responded well to the treatment and her side effects healed.

Discussion: To our knowledge this is the first case to report on concurrent palbociclib and radiation use, with resultant enhanced radiation effects that required hospitalization for symptom management. Several preclinical studies have shown synergistic effects of radiation and both *in vivo* and *in vitro* experiments resulting in improved survival and decreased cell proliferation, respectively, through enhanced G1 cell cycle arrest.

Conclusion: This case highlights the importance of using caution when combining radiation with the new targeted therapies. Until more data becomes available, physicians are recommended to exercise clinical judgment when deciding on whether to continue or discontinue a CDK4/6 inhibitor in a patient who may need radiation.

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1. Introduction

Cyclin-dependent kinase (CDK) 4/6 inhibitors represent a new class of targeted therapy options for the treatment of estrogen receptor-positive (ER+) human epidermal growth factor 2-negative (HER2−) metastatic breast cancer either as initial therapy or after disease progression on endocrine therapy.[1,2] In a phase 2 study, the addition of palbociclib to letrozole compared to placebo-letrozole showed significantly improved progression-free survival (24.8 *vs.* 14.5 months, $P<0.001$) in women with advanced ER+, HER2− breast cancer.[2] Their relatively recent approval means that our experience with these agents is not extensive, especially when they are used in more unique and complex situations. As per the study protocol leading to palbociclib approval, palliative radiotherapy was permitted for the treatment of painful bony lesions and palbociclib treatment was to be interrupted during radiotherapy, stopping 1 day before and resuming treatment 1 week after.[2,3] Here we describe the case of a patient with metastatic breast cancer who received radiation treatment to a metastatic supraclavicular lymph node while on palbociclib, a selective inhibitor of CDK4/6, and developed left neck pain that progressed to a severe skin breakdown in the area where radiation therapy was directed, resulting in the need for hospitalization.

2. Case presentation

A 62-year-old postmenopausal female was diagnosed with Stage IV (T0, N3, M1) ER+/PR+/HER2− invasive lobular breast cancer with metastasis to lymph nodes, rectus muscle, bilateral extraocular muscles, and brain. Her metastasis to the 4th ventricle was successfully treated with stereotactic radiosurgery to 25 Gy in 5 fractions two years prior to presentation, which she tolerated well. After Anastrazole therapy for over one year, a CT scan confirmed continued progressive disease in the left neck arising behind the sternocleidomastoid muscle in the parajugular chain lymph node stations, extending from the hyoid bone superiorly down to the left prepectoral and upper axillary region. An excisional biopsy of the left supraclavicular lymph node confirmed progression, and patient was switched to treatment with fulvestrant 500 mg intramuscular injections every 28 days with palbociclib 125 mg capsule taken daily for three weeks on one week off every 28 days. Five months into treatment, CT Neck and PET/CT showed response with no areas of disease remaining besides posterior neck and supraclavicular regions that patient continued to describe as painful (Fig. 1). Decision was made to treat the area with radiation. Patient continued to take palbociclib throughout radiation treatments.

Treatment was started using three-dimensional conformal radiotherapy (RT) to her left neck with plans to complete 60 Gy in 30 fractions (200 cGy/fraction) as this was the only site of disease shown on imaging (Fig. 2). After five fractions, she developed odynophagia concerning for radiation esophagitis, significantly earlier than is typically observed. After 20 fractions, she developed moist desquamation and hyperpigmentation of the skin consistent with grade 2 radiation dermatitis (CTCAE v4.0, Fig. 3, patient provided informed written consent for publication of clinical images). She was treated with viscous lidocaine, pain medication, petrolatum skin ointment, and silver sulfadiazine. The physics staff performed *in vivo* dose measurement of the radiation output of the linear accelerator by placing a NanoDot Optically Stimulated Luminescence detector on the left supraclavicular skin with a result of 198.770 cGy which was within appropriate tolerance of expected output. Her symptoms continued to worsen to the point that she could not maintain hydration or nutrition due to odynophagia, grade 3 esophagitis, and outpatient IV hydration had to be arranged. Her skin began to

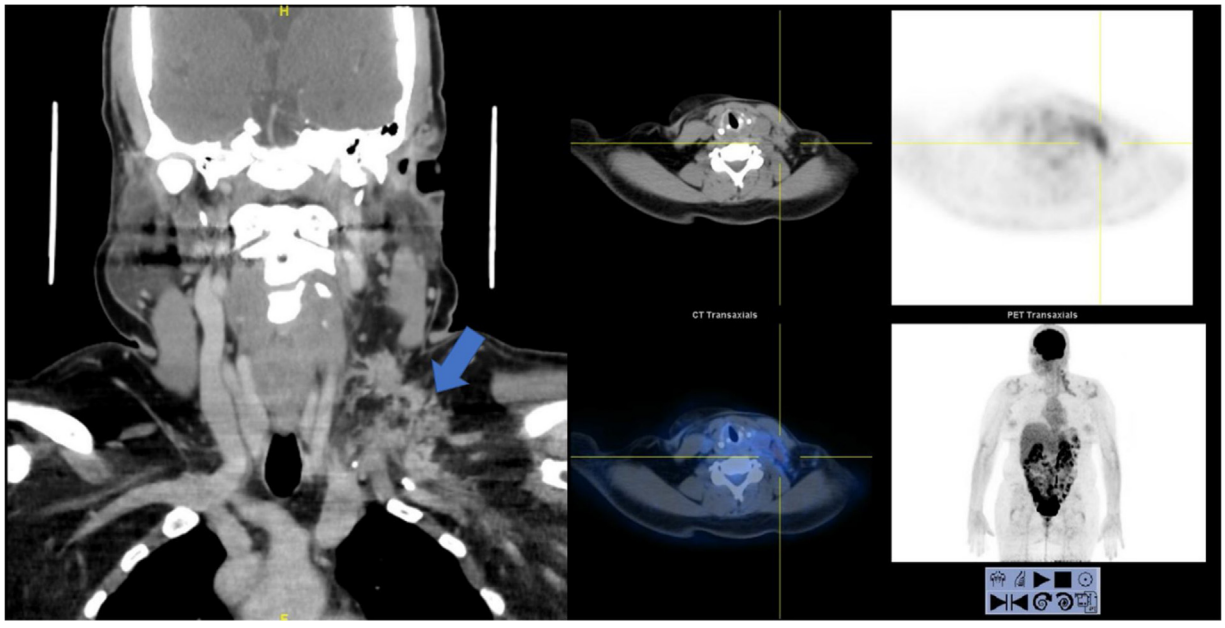
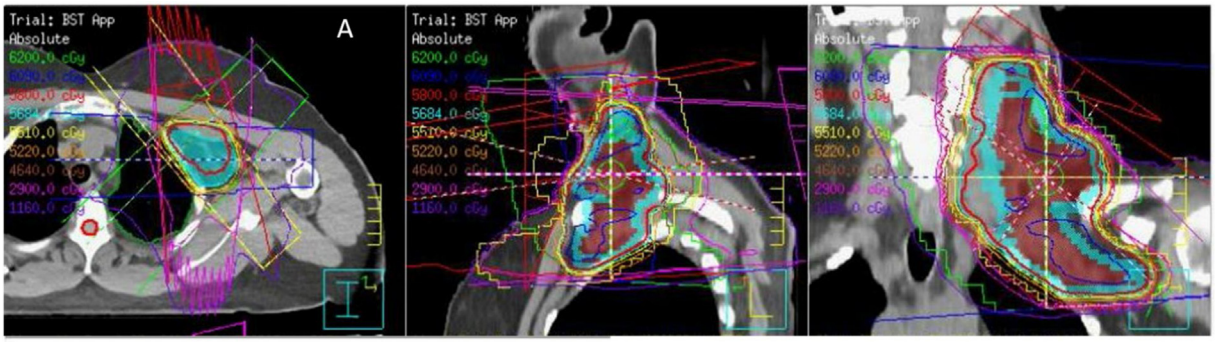
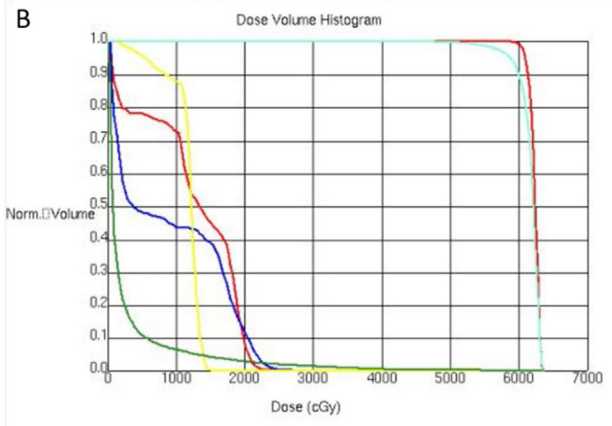


Fig. 1 – Pre-treatment CT Neck (left) and PET/CT (right) scans demonstrate the only area of active disease to be in left supraclavicular area.





ROI Statistics

Line Type	ROI	Trial or Record	Min.	Max.	Mean	Std. Dev.
	Cord	BST App	39.5	2502.6	1236.5	699.6
	Esophagus	BST App	32.9	2702.4	902.2	841.1
	GTV_dose	BST App	5592.7	6354.6	6226.9	73.7
	Humeral Head	BST App	112.4	1513.1	1162.8	245.8
	Lung_L	BST App	6.9	5441.8	256.7	556.5
	PTV_6000	BST App	1327.4	6366.1	6163.1	204.2

Fig. 2 – A) Isodose lines shown in axial, sagittal, and coronal planes with the planned total dose of 60 Gy in 30 fractions using 3D-CRT on TrueBeam linear accelerator. B) DVH showing prescription and normal structures with emphasis on mean esophagus dose about 9 Gy.

slough off, grade 3 dermatitis, (CTCAE v4.0, Fig. 4) and the decision was made to hold radiation and palbociclib, and admit her to the hospital for pain control, IV fluids, and wound care. After discharge, she was seen in a follow up clinic visit 1 month after discontinuation of radiation. The desquamation had resolved, but hyperpigmentation of the treated area remained (Fig. 5). Patient was able to finish her 10 remaining radiation treatments to a dose of 20 Gy (total of 60 Gy) without resuming palbociclib which she tolerated well. Clinically, her tumor softened and shrank at therapy completion. She restarted palbociclib one month after completion of RT. At six month follow up, she had no evidence of disease based on imaging and continued palbociclib and fulvestrant without side effects.

3. Discussion

Concurrent delivery of chemotherapy and radiation has shown improved survival in certain cancers compared to sequential delivery such as non-small cell lung cancer.[4] The survival benefit in this Phase III clinical trial was linked to the radiosensitizing antitumor effect of concurrent cisplatin. The acute toxicity was statistically significantly worse with concurrent chemoradiation, but long-term toxicity was comparable. New systemic agents, such as checkpoint blockade immunotherapy, have shown synergistic effects on local and distant tumor control when radiation is used in combination.[5] The immune system plays an important role in tumor cell death in the radiation field, mainly mediated by CD8 T cells. Radiosensitization from immunotherapy is facilitated by increased antigen presentation from radiation effects on tumors. Radiosensitization from chemotherapy is multifactorial including inhibition of sublethal DNA damage repair and synchronizing cells to a particular phase of the cell cycle that is more susceptible to radiation.[6,7]

Palbociclib alone has been shown to cause rash of any grade in 16.5% of patients and mucosal inflammation in 28.9%.[8] Esophageal dose constraint based on Quantec is mean <34 Gy

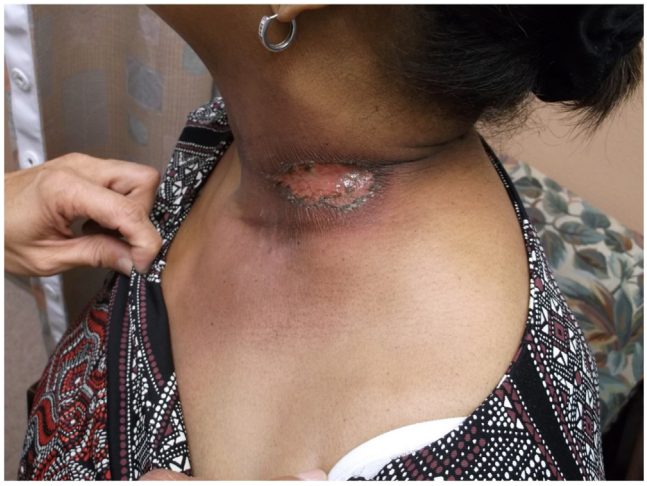


Fig. 3 – Radiation dermatitis in left neck region after 20 fractions of radiation. Radiation treatments were held.

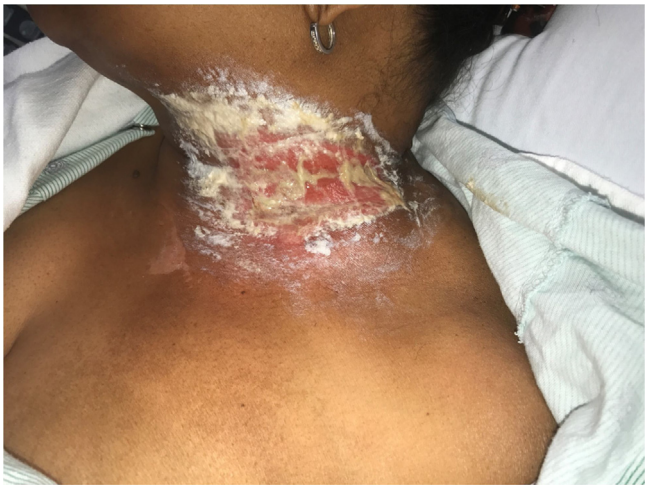


Fig. 4 – Worsening radiation dermatitis about one week later requiring hospital admission.

leading to grade 3+ esophagitis in 5–20%, which our dose was well below.[9] There are no published prospective data on the safety of use of radiation treatment with palbociclib. A recent case series reported results on five metastatic breast cancer patients who were treated with concurrent palbociclib and radiation; four had metastasis to the bone and one had metastasis to the liver.[10] Radiotherapy was indicated for symptom management in all five patients. In this case series all patients were reported to experience symptom control with excellent pain relief. Reported toxicities included low-grade mucositis in two patients, and hematologic toxicities in all patients comparable with published literature. No skin toxicities were observed. The authors concluded that combination of palbociclib and radiation did not result in increased toxicity. However, the bone radiation course was 20 Gy in 5 fractions which is a lower dose than our case. The liver radiation dose was 60 Gy in 10 fractions which is consistent with radiosurgery and, therefore, the liver metastasis was able to be treated to high dose without affecting nearby normal tissue. Our patient had the

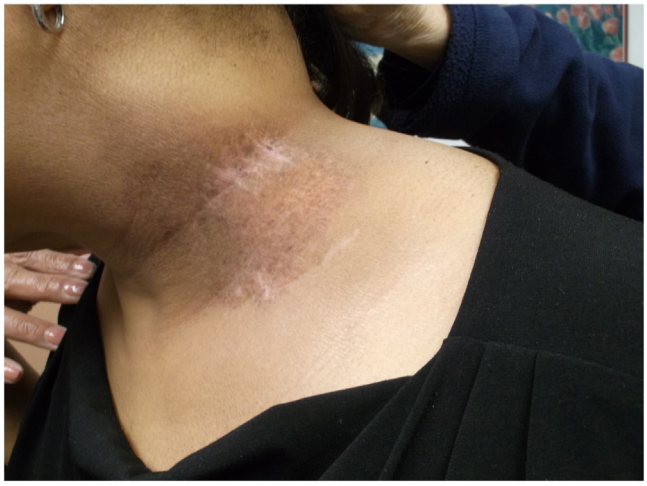


Fig. 5 – Left neck region 1 month after holding radiation showing resolution of desquamation, but persistent hyperpigmentation.

esophagus and skin nearby the prescription isodose line, making these structures more difficult to avoid and increasing likelihood of significant toxicity. Another recent case report from Japan demonstrated grade 3 colitis in a patient with metastatic breast cancer undergoing concurrent palbociclib and radiotherapy of 30 Gy in 10 fractions to the left iliac bone and first sacral vertebrae.[11] The case was the first reported evidence of normal tissue over-sensitisation secondary to palbociclib combined with radiation. Ribociclib is another CDK 4/6 inhibitor that has been studied with Letrozole and concomitant palliative radiotherapy.[12] The preliminary experience of five patients with bone and/or visceral metastases (2 lung, 1 liver) from breast cancer treated with 20–30 Gy in 5 fractions showed no significant adverse effects and no suspension of RT course.

To our knowledge, this is the first case to report on concurrent palbociclib and radiation use, with resultant enhanced radiation effects of dermatitis and esophagitis that required hospitalization for symptom management. Her heightened response to radiation was suggested to be explained by the radiosensitizing effects of palbociclib seen in preclinical studies.[13] The CDK4/6-cyclin D1 complex is an important mediator of the cell cycle from G1 phase to S phase where DNA synthesis occurs.[14] Unphosphorylated retinoblastoma (RB) protein binds to E2F transcription factor and prevents upregulation of genes that promote cell growth. Phosphorylated RB protein releases E2F and allows it to upregulate cell cycle genes. Inhibition of CDK4/6 leads to decreased phosphorylation of RB protein and subsequent G1 cell cycle arrest. The cells eventually undergo senescence and apoptosis. Several preclinical studies have shown synergistic effects of radiation and palbociclib in GBM, medulloblastoma, and Rb-proficient brain tumors both in *in vivo* and *in vitro* experiments resulting in improved survival and decreased cell proliferation, respectively, through enhanced G1 cell cycle arrest.[15–19] Similar results were found in human prostate cancer models.[20] Another study in genetically engineered mice were found to have exacerbated acute gastrointestinal toxicity when treated

with fractionated radiation plus concurrent palbociclib compared to radiation alone.[21] Interestingly, palbociclib has been shown to be a potential protector against radiation in mice regarding lethal gastrointestinal injury after 15 Gy total body irradiation.[22] The behavior of palbociclib as a radiation sensitizer or protector seems to be dependent on the fractionation of radiation and should be explored further to realize potential clinical benefits.

4. Conclusion

Many drugs with targeted antitumor cellular pathways are moving forward in clinical trials. While the drugs with promising systemic activity are mainly indicated for Stage IV disease, their potential use as radiosensitizers is being explored. This trend highlights the importance of using caution when combining radiation with the new targeted therapies. Until more data becomes available, physicians are recommended to exercise clinical judgment and individualize patient treatments when deciding on whether to continue or discontinue a CDK4/6 inhibitor in a patient who may need radiation.

Conflict of interest

None declared.

Financial disclosure

None declared.

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