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Original Research

Enhanced toxicity with CDK 4/6 inhibitors and palliative radiotherapy: Non-consecutive case series and review of the literature

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ABSTRACT

Current first-line systemic treatment in most patients with metastatic hormone receptor-positive, HER-2 negative breast cancer is an aromatase inhibitor in combination with a cyclin dependant kinase (CDK) 4/6 inhibitor. Frequently, these patients require palliative radiotherapy (RT) for symptomatic disease management. There is a paucity of data on the safety of combining a CDK 4/6 inhibitor with palliative RT, with conflicting case reports in the literature. We report on 5 cases at our institution where enhanced radiotherapy toxicity was observed when palliative doses of RT was delivered during or prior to treatment with a CDK 4/6 inhibitor. After review of pre-clinical and mechanistic data, we hypothesise that the effects of CDK4/6 inhibition on normal tissue and the tumour microenvironment may impede tissue recovery and exacerbate acute radiation and radiation recall toxicities. Further studies are required to clarify the potential toxicities of this combination. Clinicians should consider the potential risks when combining CDK 4/6 inhibitors with palliative RT and individualise patient management accordingly.

Introduction

The current standard of care for the first-line treatment of metastatic hormone receptor-positive, HER-2 negative breast cancer is an aromatase inhibitor (AI) in combination with a cyclin dependant kinase (CDK) 4/6 inhibitor. This is based on three recently published randomised trials demonstrating a progression-free survival benefit in favour of this combination compared with AI monotherapy [1–3]. Palbociclib, ribociclib and abemaciclib are potent and specific inhibitors of CDK4 and CDK6 with a more favourable toxicity profile compared with non-selective CDK inhibitors. Myelosuppression is the most commonly reported toxicity seen in up to 80% of women on palbociclib or ribociclib and up to 50% on abemaciclib. Other common toxicities include fatigue, nausea, diarrhoea, increased liver enzymes and skin toxicities [1–4].

Palliative radiotherapy (RT) is often indicated for symptomatic disease management in patients with metastatic breast cancer (mBC). There is limited and conflicting data on the potential synergistic toxicities of palliative radiotherapy and CDK 4/6 inhibitors. Some small case series indicate that the combination is safe [5–8], whilst other investigators have reported enhanced toxicities with the combination [9, 10].

Here, we report five cases of augmented toxicities in patients who received palliative RT and a CDK4/6 inhibitor. We reviewed the current literature, preclinical data, and postulate potential synergistic mechanisms for the enhanced toxicity. These cases were identified by a retrospective chart review over a three-year period where CDK 4/6 inhibitors were prescribed at our institution. In total, 63 patients received a CDK 4/6 inhibitor, twenty-six (41%) received palliative radiotherapy either during or prior to commencement of a CDK 4/6 inhibitor.

Case series

Case 1

A 43-year-old woman presented with localised hormone receptor positive breast cancer (BC), and was managed with breast conservation surgery, adjuvant chemotherapy, whole breast irradiation and adjuvant endocrine treatment (tamoxifen). She relapsed within the breast

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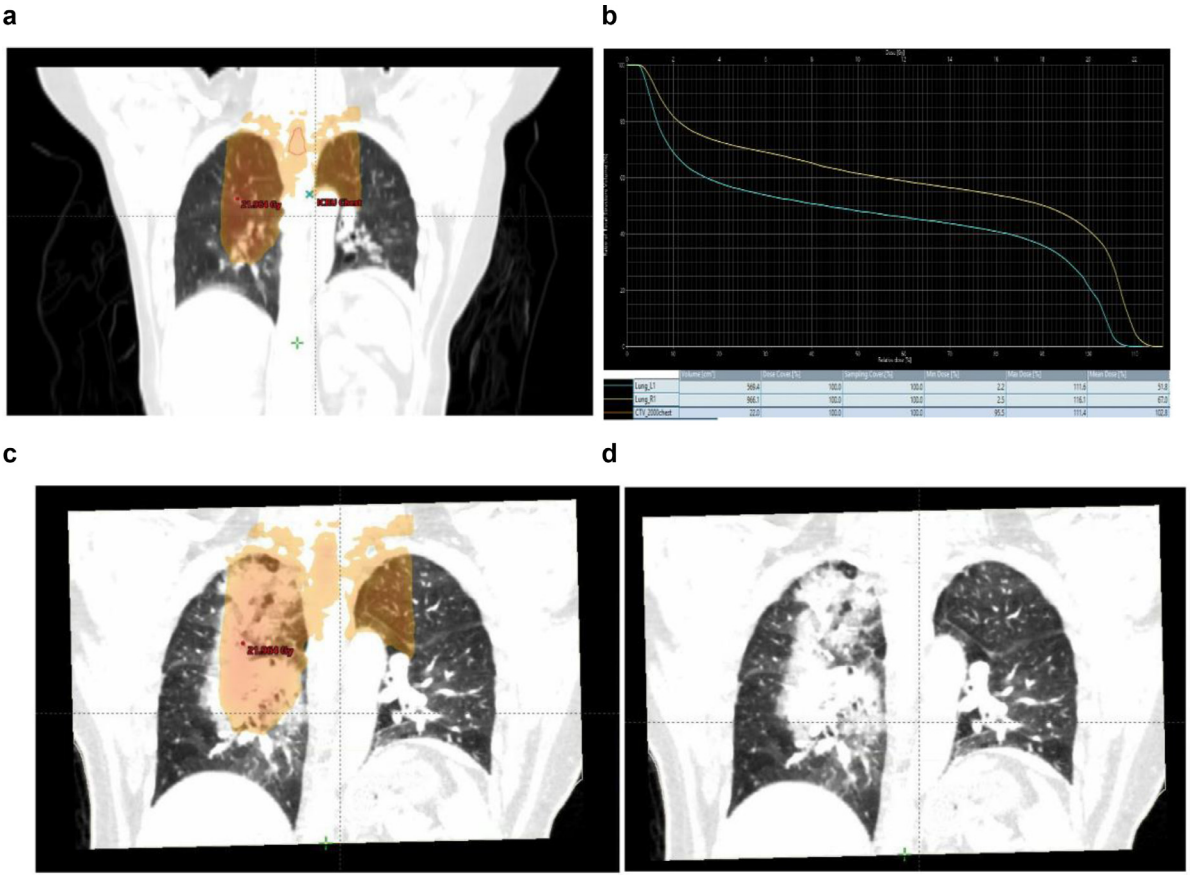

Fig. 1. a. Irradiated lung volume (dose cloud, representing 20 Gy), using an anterior posterior beam arrangement to a dose of 20 Gy in 5 fractions.
b. Dose volume histogram of left lung (labelled Lung_L1) and right lung (labelled Lung_R1)
c. Pneumonitis, shortly after commencing Palbociclib.
d. Correlation between pneumonitis and 20 Gy dose cloud.

ten years later and was managed with a mastectomy and switched to an AI. Two years later, she developed mBC and was commenced on fulvestrant. At subsequent progression she was switched to everolimus in combination with exemestane. At further progression, she received multiple lines of chemotherapy including capecitabine, vinorelbine, nanoparticle albumin-bound paclitaxel, eribulin and liposomal doxorubicin.

Nine years after the first onset of mBC, she received palliative RT, 20 Gy in 5 fractions to symptomatic mediastinal nodal metastases causing a persistent cough, shortness of breast and occasional hemoptysis. A standard anterior and posterior radiotherapy beam arrangement was used. The mean lung dose to the right lung was higher than the left lung (Table 1), because of partial cardiac shielding, reducing the dose delivered to the left lung (Fig. 1a), which has been depicted in a dose volume histogram (DVH), Fig. 1b. She had symptomatic improvement in the weeks following her treatment with a reduction in her cough, shortness of breath and hemoptysis.

Four months after radiotherapy, she commenced on self-funded palbociclib 125 mg/daily concomitant with letrozole, being aware of the paucity of data on CDK4/6 therapy in the late-line treatment setting. Within one week of palbociclib therapy, the patient developed rapidly progressive shortness of breath. CT imaging revealed right lung ground glass opacity prominently in the distribution of previous radiation field (Fig. 1c and d). Palbociclib was ceased promptly. Despite high dose antibiotics and steroids she became hypoxic. Bronchoscopy findings confirmed diffuse inflamed mucosa, on the right bronchial tree with frothy white secretions. She became oxygen-dependant and was transferred to hospice with significant respiratory failure and functional decline.

The cause of death was treatment-related Grade 5 pneumonitis, which we postulate was a radiation recall reaction secondary to palbociclib.

Case 2

A 54-year-old post-menopausal woman presented with *de novo* metastatic hormone receptor-positive HER-2 negative lobular BC involving the right axillary nodes, adrenal glands and skeleton. She received three cycles of first-line palliative chemotherapy, whilst overseas (docetaxel, adriamycin and cyclophosphamide). Following satisfactory chemotherapeutic response, she continued on AI (letrozole) and bisphosphonate therapy. At the onset of disease progression, palbociclib was commenced in combination with ongoing letrozole. Twelve months later a bone metastasis in the right femoral neck required prophylactic pinning and palliative RT, 20 Gy in 5 fractions. Palbociclib therapy was ceased one day before RT and was recommenced one week after the completion of RT. No immediate or late radiation toxicities were observed to the hip or overlying skin.

Four months later she developed further progression evidenced by multiple small, biopsy-proven cutaneous nodules over the right breast. She received palliative RT, 36 Gy in 12 fractions to the whole breast, using medial and lateral tangential fields, consisting of 6MV photon fields with a 25% contribution from an 18-MV field-in-field boost. Electrons were not used in the treatment plan. Bolus, with a thickness of 5 mm was placed over the breast for the entire treatment course. Palbociclib was withheld during and recommenced one week after radiotherapy. At the end of the treatment the skin overlying the breast was erythe-

Table 1
Summary of clinical cases and relationship between palbociclib dosing and radiation.

Case	Age (yr)	Radiation site and dose (Gy)/fraction	Palbociclib dose	Interval between CDK 4/6 and radiation	Adverse event and grading	Radiation dose to organs at risk
1	43	Chest, 20 Gy/5 fractions	125 mg daily	4 months after	Grade 5 pneumonitis	Lung V20 = 33%; MLD left lung = 10 Gy; MLD right lung = 13Gy
2	54	Right breast, 36 Gy/12 fractions	125 mg daily	1 day before	Grade 3 dermatitis	Breast PTV: max dose = 36.7Gy
3	44	T-spine, 30 Gy/10 fractions	125 mg daily	None, (concurrent)	Grade 3 oesophagitis	Oesophagus: max dose = 27.8 Gy; mean dose = 26.0 Gy
4	51	T-spine, 20 Gy/5 fractions	125 mg daily	5 days prior, 2 weeks after	Grade 2 dermatitis	Skin: V10 = 2.5%, V20 = 1%
5	70	C-spine, T-spine 20 Gy/5 fractions	125 mg daily	1 week before	Grade 3 oesophagitis	Oral Cavity: mean dose = 3.9 Gy; max dose = 20.2Gy

Abbreviations: V20 – Volume of organ (%) receiving ≥ 20 Gy; V10 - Volume of organ (%) receiving ≥ 10 Gy; max = maximum; MLD = mean lung dose.

matous. Within five days of recommencing palbociclib (twelve days after radiotherapy), the patient developed severe cutaneous desquamation over the treated area. Palbociclib was ceased. The Grade 3 radiation skin toxicities settled 10 days later with antibiotics and wound dressings. Antibiotics were prescribed by the treating radiation oncologist given the severity of the skin reaction and concern about the possibility of a concomitant infection. At no time did the patient develop a fever or display signs of systemic infection. Bacterial cultures were not performed.

Case 3

A 44-year-old premenopausal woman with locally advanced hormone receptor-positive, HER-2 negative BC was treated with neoadjuvant chemotherapy (5-fluorouracil, epirubicin and cyclophosphamide), mastectomy with reconstruction followed by adjuvant RT and adjuvant endocrine therapy (AI) with ovarian suppression (a lutenising hormone-releasing hormone agonist, goserelin). Eight years later, she developed mBC. Biopsy-proven bony metastases of the same phenotype in the T5 vertebral body with left-sided soft tissue extension was visible on CT and FDG- PET imaging (Fig. 2a and b). She was commenced on first line letrozole in combination with palbociclib. She continued on palbociclib while receiving palliative RT, 30 Gy in 10 fractions – with dose to the oesophagus and lungs depicted in a DVH, Fig. 2c. Within six days of completing palliative RT, Palbociclib was ceased due to Grade 3 oesophagitis. Severe odynophagia, dysphagia and fatigue necessitated admission to hospital for supportive care. The patient made a complete recovery and was recommenced on palbociclib.

Case 4

A 51-year-old perimenopausal woman was diagnosed with *de novo* mBC with widespread metastatic bone disease. A core biopsy of a left breast lesion confirmed a grade 2 strongly hormone receptor-positive and HER-2 negative carcinoma. She had symptomatic hypercalcaemia treated with bisphosphonate therapy. She received palliative RT, 20 Gy in 5 fractions to painful bony disease in the cervical and thoracic vertebrae (C1–3 and T3–5). Palbociclib was commenced (100 mg daily then 125 mg at cycle 2) in combination with letrozole and ovarian suppression (goserelin).

Twelve months later, a routine CT scans demonstrated isolated disease progression at the T8 vertebra. She received palliative RT, 20 Gy in 5 fractions to this new site. Palbociclib was withheld for five days prior to palliative RT. Four days after completing RT she developed Grade 2 skin reaction in a well-defined area of marked skin desquamation within the radiotherapy field characterised by marked skin desquamation (Fig. 3). She recommenced palbociclib at 125 mg after the resolution of skin toxicities with no further issues.

Case 5

A 70-year-old woman had a Grade 3 hormone receptor-positive and HER-2 negative early BC, treated with wide local excision, axillary clearance, adjuvant anthracycline-based chemotherapy, adjuvant RT and an AI for five years. Eleven years later, she developed widespread bone metastases, hilar and mediastinal lymphadenopathy confirmed on PET and CT imaging. Mediastinal lymph node biopsies confirmed GATA-3 positive, hormone receptor-positive and HER2-negative invasive carcinoma of same phenotype as the original BC.

She received palliative RT, 20 Gy in 5 fractions to painful metastases in the T12-L4 vertebrae and commenced on an AI (letrozole). Two months after radiotherapy, she commenced on palbociclib within a Phase 4 clinical trial. Five months later, she reported new back and neck pain requiring further palliative RT, 20 Gy in 5 fractions to new sites in C1–3 and T1–3 vertebrae. Palbociclib was ceased for 3 weeks during RT. However, on the final day of RT she developed Grade 3 oesophagitis. Severe oral mucositis and odynophagia necessitated parenteral opioids

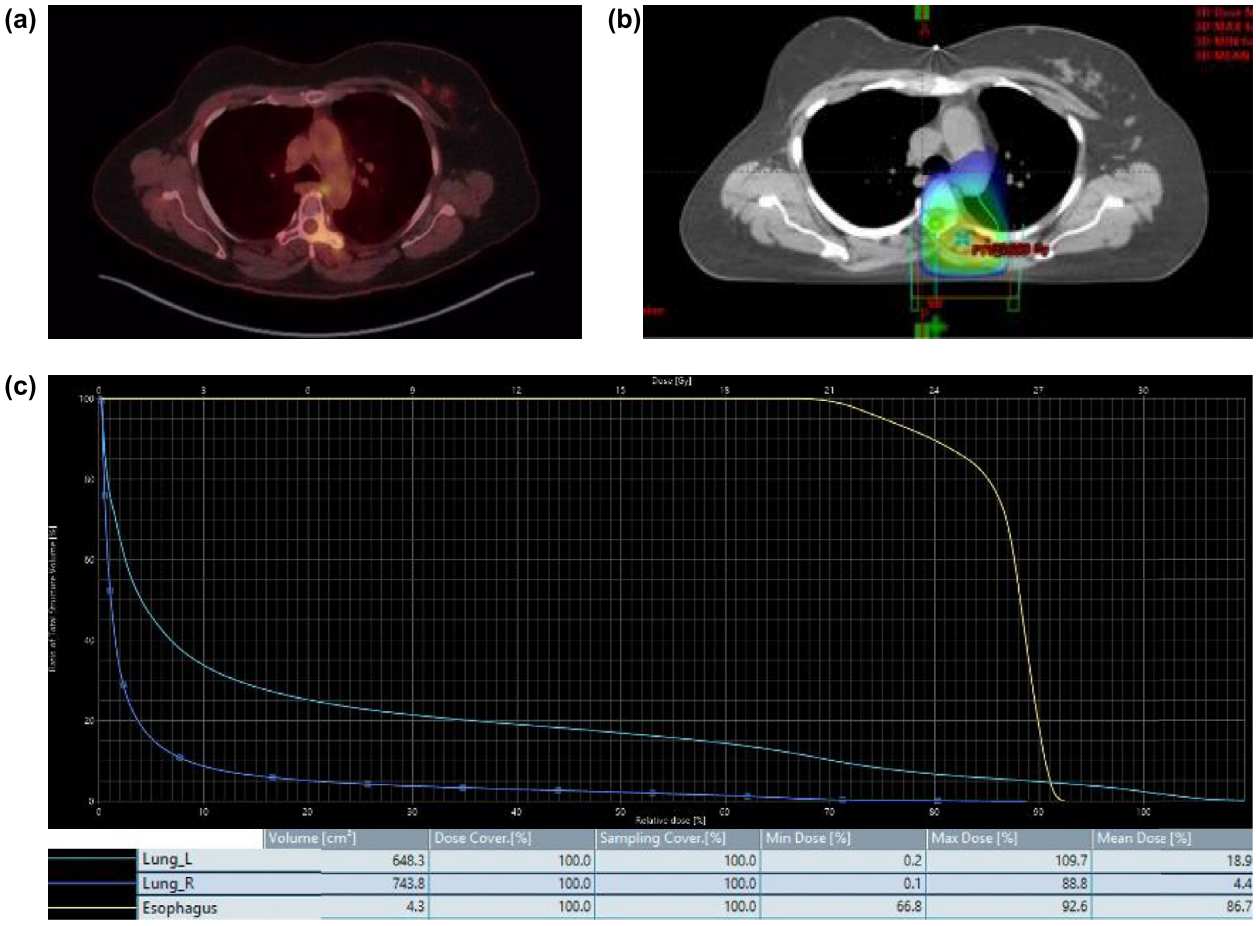

Fig. 2. a: FDG-PET scan demonstrating uptake within the oesophagus, consistent with the esophagitis
b: The 30 Gy dose cloud, delivered with a single posterior beam
c: Dose Volume Histogram showing dose to left lung (Lung_L), right lung (Lung_R) and oesophagus.

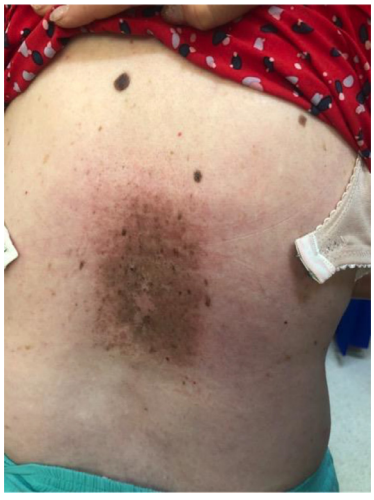

Fig. 3. skin reaction, 4 days after completing a dose of 20 Gy in 5 fractions to the thoracic spine, using a single posterior field.

and other supportive measures, including intravenous-fluids during her nine-day hospital admission. While the dose to the oral cavity and superior pharynx was above mucosal tolerance (depicted in DVH, Fig. 4), the rapidity of onset and the severity of the toxicity appears to be in excess of what would be expected with this palliative regimen.

Discussion

Whilst many systemic anti-cancer therapies are associated with enhanced radiation toxicity to normal tissues and also associated with radiation recall [11], there is limited experience and published data on the safety of concomitant radiation and CDK4/6 inhibitors. Herein, we provide five examples where exaggerated toxicity was observed with palliative-intent RT and palbociclib, including one case of fatal pulmonary toxicity. Additionally, we observed skin and mucosal toxicity in excess of our clinical expectations. All patients received concomitant AI therapy with or without goserelin. Of note, the timing of palbociclib administration and the dose and site of RT varied between the cases (Table 1). Rapid onset of severe pneumonitis occurred within one week of palbociclib initiation, four months after RT to the chest and mediastinum (20 Gy in 5 fractions) in Case 1. The authors acknowledge that this patient also received everolimus (known to be associated with pneumonitis), however the drug was received seven years prior to radiotherapy, thus making this less likely to be the causative factor. Although pneumonitis is rarely associated with palbociclib monotherapy, localization to the high dose region of the radiation field, together with the temporal relationship between its commencement and the rapid onset of the pneumonitis would suggest a radiation recall phenomenon. The unilateral nature of the pneumonitis is likely explained by the higher mean lung dose on the right side (Table 1) due to cardiac shielding of the left lung; the increased dose delivered to the right lung is also depicted in the DVH (Fig. 1b). The authors acknowledge that whilst there was previous radiotherapy to the breast, this was ten years earlier and

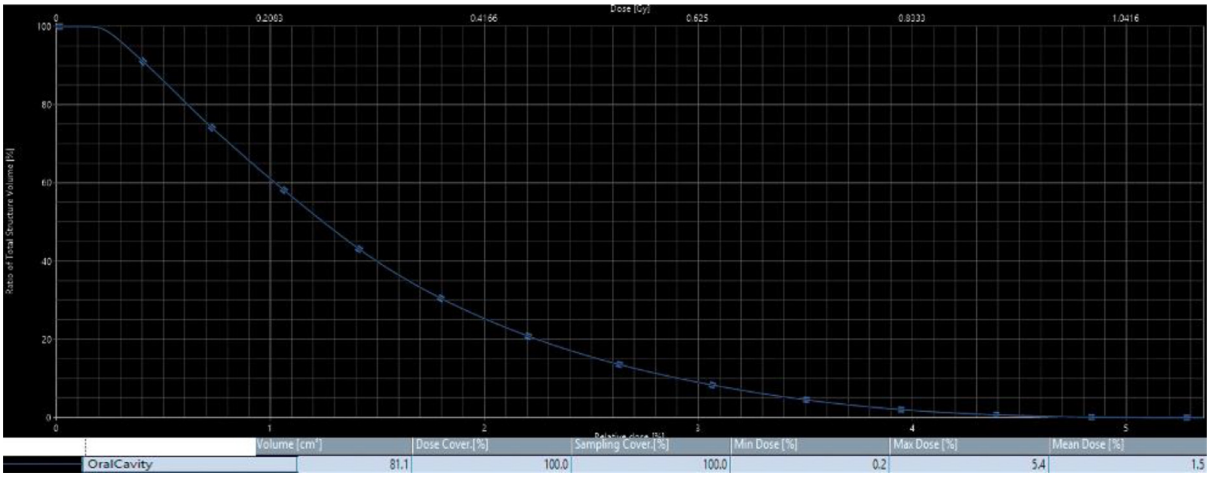

Fig. 4. Dose Volume Histogram showing dose oral cavity.

although possible, was unlikely to be a contributing factor to the pneumonitis. In Case 3, palbociclib was given concurrently with RT (C-spine, 30 Gy in 10 fractions) with resultant grade 3 oesophagitis first noted six days following RT completion. Cases 2, 4 and 5 arose in patients on established palbociclib therapy whose treatments were withheld during RT. With the exception of case 1, all patients recovered from their acute radiation toxicities, and no late toxicities have been observed. Of note, in Case 2 no enhanced toxicity was reported when the patient received radiotherapy to the hip. This is possibly explained by the fact that palliative doses of radiotherapy to the bone is mostly well tolerated.

Messer et al. reported on a 62-year old patient who developed early onset RT-related oesophagitis and dermatitis following RT to supraclavicular nodal disease (60 Gy in 30 fractions) while receiving palbociclib (125 mg daily) and fulvestrant [9]. Grade 3 radiation-related enterocolitis was observed in a 58-year old patient with mBC following RT (30 Gy in 10 fractions) to the left iliac bone and upper sacrum and concurrent palbociclib (100 mg daily) and fulvestrant [10]. Conversely, a number of case series described combining RT with CDK 4/6 inhibitors as safe and well-tolerated [5–8]. To our knowledge, this is the largest series of cases reporting enhanced toxicity when combining radiotherapy with a CDK 4/6 inhibitor.

The cyclin D1-CDK 4/6 complex is implicated in extracellular signalling pathways essential in cell cycle progression through the G1–S phase via the phosphorylation of retinoblastoma (Rb) proteins and the release of key transcription factors, such as E2F family proteins [12]. The deregulation of key components in these pathways including the functional loss of Rb is highly prevalent in breast cancer. Oestrogen signalling is known to upregulate cyclin D1 levels and mediates multiple mitogenic processes converging on the cyclin D1-CDK 4/6 axis, leading to the promotion of cell cycle progression, thus forming the rationale of targeting CDK 4/6 [13–15]. A main mechanism of action of CDK4 /6 inhibition is thought to be cell cycle arrest with resultant tumour cell quiescence or senescence. Aside from reinforcing cytostasticity, loss of CDK 4/6 activity may also have other cellular implications such as altered cellular metabolism, disruption of reactive oxidative species (ROS) clearance and initiation of apoptosis. Interestingly, a recent study demonstrated that CDK 4/6 inhibition affected the maturation processes of immune system sentinel cells (e.g. neutrophils and regulatory T-cells) [16].

Ionising radiation causes both direct deoxyribonucleic acid damage and indirect cellular damage by generation of ROS, and may lead to tumour cellular death by various means including apoptosis, necrosis, autophagic cell death and mitotic catastrophe [17–19]. The cellular effects of RT including bystander effects on normal tissues and the tumour microenvironment following tissue damage are highly dependant on tissue type and varies between individuals [20]. Early effects (during or within weeks of radiation) often involve pro-inflammatory pathway activation characterised by pro-fibrotic cytokines, vascular injury and the coagulation cascade with initiation of early healing processes. Late effects (months or even years after radiation) are characterised by delayed onset fibrosis, cellular death, atrophy and vascular damage, partly due to an adaptive response to acute tissue damage. These processes may be perpetuated by cell loss and dysregulated interactions between new repopulating cells and/or hypoxia. Both early and late radiation effects on normal tissue can lead to the creation of an inflammatory milieu within the tumour micro-environment with the attraction of pro-inflammatory immune cells [18].

We hypothesise that the effects of CDK 4/6 inhibition on normal tissue and the tumour microenvironment may impede tissue recovery and exacerbate acute radiation and radiation recall toxicities (Fig. 5). Mechanisms may include inappropriate cell cycle arrest during cellular repair, effects on cellular metabolism, and loss of cellular ROS scavenging and elimination abilities. These processes may even lead to late radiation-related tissue damage in otherwise normal tissue [21]. Moreover, within the tumour microenvironment, CDK 4/6 inhibition may further augment anti-tumour immunity via activation of sentinel innate immune cells, thereby inducing local tissue damage [22, 23]. Preclinical studies have reported on the radiosensitising effects of CDK 4/6 inhibition in glioblastoma patient-derived cell lines and prostate cancer cell lines, and survival was extended when the two treatments were combined in glioblastoma mice models [24, 25]. While one study demonstrated the protective role of CDK 4/6 inhibition against radiation-induced intestinal injury in mice, another found that palbociclib before a single dose of subtotal body irradiation was protective but palbociclib before and during five daily fractions of irradiation exacerbated gastrointestinal injury in mice [25, 26].

The above five cases highlight the importance of clinical vigilance when administering palbociclib either concurrently or after radiation. Although the vignettes reported all pertain to palbociclib – (the first approved CDK 4/6 inhibitor) - it is foreseeable that other CDK 4/6 inhibitors, owing to similar mechanistic actions may be associated with analogous effects. CDK 4/6 inhibitors are now a mainstay of treatment in mBC and their role in the adjuvant setting, in second line and beyond and other tumour types are also being actively investigated, underscoring the importance of understanding their safety profile when used in conjunction with radiotherapy.

These five cases (19%) were identified from a total of twenty-six patients who received palliative RT either prior to, or concomitantly with treatment with a CDK 4/6 inhibitor. We acknowledge that this is

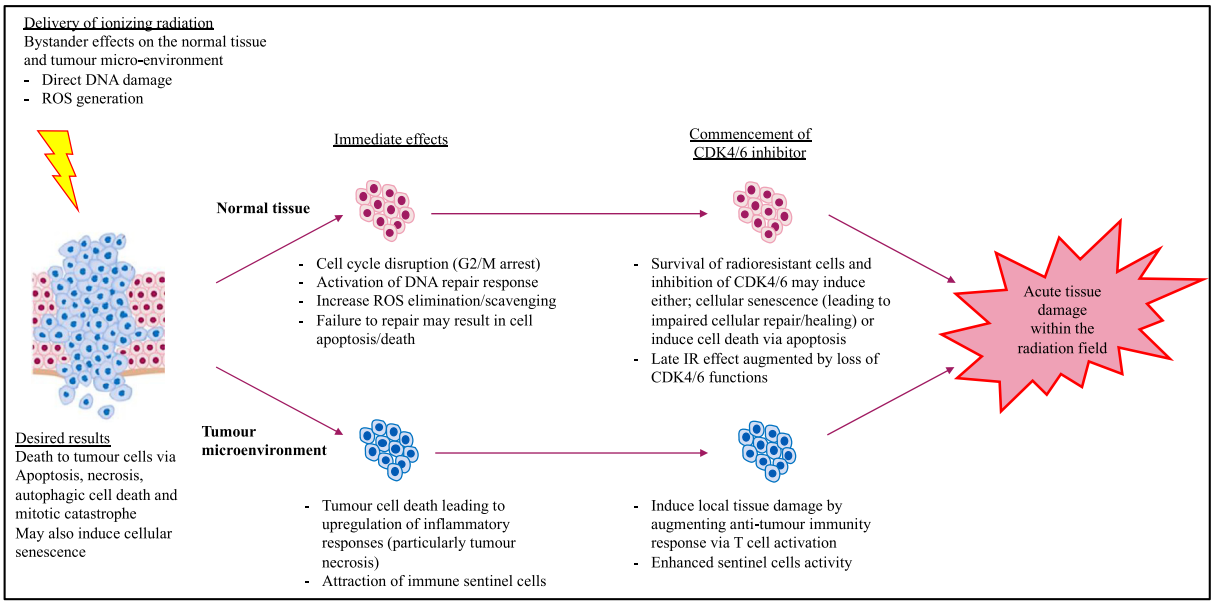

Fig. 5. Proposed mechanisms of tissue damage when combining CDK 4/6 inhibitors with radiation.

a retrospective analysis but this represents a not insignificant rate of enhanced toxicity worthy of further study.

In particular, a few clinically pertinent questions warrant careful study. First, what is the optimal timing of CDK 4/6 inhibitor administration before, during and after RT? If concurrent use is to be avoided, what then is an appropriate washout period of the CDK 4/6 inhibitor, conceivably to allow bystander tissue damage recovery or reduction of reactive immune cells within the radiation field? As suggested in preclinical studies, fractionation and scheduling of radiation will likely also play a role and requires further evaluation. Second, it is plausible that certain tissues or organs may be more vulnerable to injury. Examples include tissues that are rapidly renewing or those with continuous exposure to pathogens and consequently higher levels of innate reactive immunologic activities such as lung, skin and the gastrointestinal tract. Specific attention to these areas may be relevant for radiation planning. Third, there may be a subset of patients who are at higher risk, such as those suffering from superimposed infection or those with comorbid pathology in the radiation field for whom treatment should be carefully considered and individualised. Therefore, highly conformal radiotherapy planning techniques should be considered even when prescribing palliative intent radiotherapy to mitigate the risks of enhanced toxicity to organs at risk.

Conclusion

This case series demonstrates the potential of enhanced RT toxicity when administering a CDK 4/6 inhibitor concurrently or soon after radiotherapy. Clinicians using this combination should consider this potential when prescribing RT. Additional studies on combined CDK 4/6 inhibition and RT are required to further clarify the potential for enhanced toxicity from this combination.

Declaration of Competing Interest

None.

Funding source

None.

Ethical approval

None.

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