



Safety of cyclin-dependent kinase4/6 inhibitor combined with palliative radiotherapy in patients with metastatic breast cancer



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ABSTRACT

Introduction: Cyclin-dependent kinase (CDK)4/6 inhibitor is a first-line therapy for metastatic ER+/HER2-breast cancer. However, there are limited data on safety of combined radiotherapy (RT) and CDK4/6 inhibition.

Methods: We conducted a retrospective study of women with metastatic breast cancer who received palliative RT within 14 days of CDK4/6 inhibitor use. The primary endpoint was toxicity per Common Terminology Criteria for Adverse Events v5. Secondary endpoints were pain response and local control based on clinical assessment and imaging.

Results: Thirty patients underwent 36 RT courses with palbociclib (n = 34 courses, 94.4%) or abemaciclib (n = 2, 5.6%). RT was delivered before, concurrently or after CDK4/6 inhibitors in 7 (19.4%), 8 (22.2%), and 21 (58.3%) of cases with median 3.5 days from RT to closest CDK4/6 inhibitor administration. Median RT dose was 30Gy (range 8–40.05Gy). Treated sites included brain (n = 5, 11.6%), spine (n = 19, 44.2%), pelvis (n = 9, 20.9%), other bony sites (n = 6, 14.0%) and others (n = 4, 9.3%). No acute grade ≥ 3 non-hematologic toxicity occurred. No increased hematologic toxicity was attributable to RT with grade 3 hematologic toxicities rates 16.7%, 0%, and 6.7% before, during, and 2 weeks after RT completion. All but one patient (29/30) achieved symptom relief. Local control rates were 94.4%, 91.7% at 6 and 12 months.

Conclusions: The use of RT within 2 weeks of CDK4/6 inhibitors had low acceptable toxicity and high efficacy, suggesting that it is safe for palliation of metastatic breast cancer.

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1. Introduction

Addition of cyclin dependent kinase (CDK) 4/6 inhibitors to endocrine therapy in hormone receptor-positive (HR+) human epidermal growth factor receptor 2-negative (HER2-) metastatic breast cancer has led to practice-changing improvements in progression-free survival [1–5], and overall survival [6,7] in the first and second-line settings. Three CDK 4/6 inhibitors (palbociclib, abemaciclib, and ribociclib) have been approved by the US Food and Drug Administration since 2015 for use in patients with HR+, HER2-advanced breast cancer. These agents work by interfering

with the transition from the G1 to S phase of the cell cycle and have been shown to preferentially inhibit HR + breast cancer cell growth, act synergistically with antiestrogens and reverse endocrine resistance [8].

These same patients with metastatic breast cancer often require palliative RT. Despite the increasing use of CDK 4/6 inhibitors, questions remain regarding the safety of the combination of CDK 4/6 inhibitor and radiation therapy (RT). Preclinical studies showed that CDK 4/6 inhibition during or after RT promoted increased tumor cell apoptosis and inhibited DNA double-strand break repair, compared to CDK 4/6 inhibition only [9]. Although the clinical trials that led to approval of CDK 4/6 inhibitors included women who received palliative RT in close temporal proximity to CDK 4/6 inhibitor use, no specific analyses were performed to evaluate toxicity in that subset of patients. Data on toxicity in this patient population are limited to a few small single-institution studies, which have shown acceptable toxicity profiles with combined

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palliative RT and CDK 4/6 inhibitor therapy [10–15].

Concerningly, case reports have highlighted a case of severe enterocolitis and a case of enhanced dermatologic toxicity associated with concurrent CDK 4/6 inhibitor use and palliative RT [16–18]. A review of literature demonstrated that more than 10% of studied patients had toxicities that were grade 3 or higher or required radiotherapy suspension [19]. The objective of this study was to evaluate the safety of combination of CDK 4/6 inhibitor and palliative RT.

2. Materials & methods

Following Institutional Review Board approval at the University of Pennsylvania, we retrospectively reviewed medical records of patients with metastatic breast cancer who were treated with palliative RT from 1/2010 to 4/2021. Patients who received RT concurrently or within 14 days of CDK 4/6 inhibitor use were included for analysis. Medical records were reviewed for patient and treatment characteristics including sex, age at time of RT, CDK 4/6 inhibitor agent, adjuvant systemic therapy, RT site, duration, dose/fractionation, and RT technique—3D-conformal RT (3D-CRT), intensity modulated RT (IMRT), volumetric modulated arc therapy (VMAT), and stereotactic body RT (SBRT). The primary endpoint of this study was toxicity during or after RT. Secondary endpoints were symptom relief and local control.

Toxicity was assessed according to the National Cancer Institute Common Terminology Criteria for Adverse Events v5 during weekly on-treatment and follow-up visits with radiation or medical oncology departments. Routine clinical laboratory tests performed up to 2 weeks before or after radiation treatment were reviewed to assess for hematologic toxicities. Pain or symptom relief was reported by the patient and local recurrences were confirmed on imaging.

Descriptive statistics were used to summarize the cohort with median and range for continuous variables and counts and frequencies for categorical variables. Data was analyzed and reported using Excel version 2105 (Microsoft, Washington, USA).

3. Results

3.1. Patient and treatment characteristics

The population consists of a total of 30 patients with metastatic breast cancer who underwent one or more courses of radiation within two weeks of CDK4/6 inhibitor use (Table 1). Five of the included patients completed more than one course of palliative RT (range 2–3 courses). The median interval from closest CDK4/6 inhibitor administration to RT was 3.5 days (range 0–14). Seven patients (19.4%) were already on CDK4/6 inhibitor and stopped prior to RT, while 8 patients received it concurrently with RT (22.2%). In other patients (n = 21, 58.3%), the closest date of CDK4/6 inhibitor use was after RT. For most RT courses (n = 34, 94.4%), patients received palbociclib. Palbociclib was given 125 mg/day for 21 days on, 7 days off. Four patients were receiving a reduced dose of 75–100 mg/day prior to RT for previously reported palbociclib-related toxicity. Abemaciclib was given 200 mg twice daily.

Details of the 36 courses of palliative RT are shown in Table 2. A total of 43 metastatic lesions were treated. The most treated site was spine (n = 19, 44.2%), followed by pelvis (n = 9, 20.9%), other bony sites (n = 6, 14.0%), brain (n = 5, 11.6%) and others (supraclavicular nodes, mediastinum, orbit, cutaneous lesion). Most of the treatment was planned with 3D-CRT with multiple fields (67.4%); IMRT or VMAT were used in 6 cases (15.0%). SBRT was used in 7 (16.3%) cases for treating bony and supraclavicular lesions (27Gy/3 fraction, 30Gy/5 fraction, 35Gy/5 fraction, 40Gy/5 fraction). One

Table 1
Baseline patient characteristics (n = 36 RT courses).

	n	%
Age at RT		
Median	59	
Range	35–80	
Days from CDK4/6 inhibitor to RT		
Median	3.5	
Range	0–14	
Medication in relation to RT		
Pre-RT	7	19.4%
Concurrent	8	22.2%
Post-RT	21	58.3%
CDK4/6 inhibitor agent		
Palbociclib	34	94.4%
Abemaciclib	2	5.6%
CDK4/6 inhibitor combined with -		
Fulvestrant	13	36.1%
AI	12	33.3%
Tamoxifen ± LHRH agonist	3	8.3%
CDK4/6 inhibitor alone	8	22.2%

Abbreviations: RT = radiation therapy; AI = aromatase inhibitor; LHRH = luteinizing hormone-releasing hormone.

Table 2
Radiation treatment details (n = 43 lesions radiated).

	n	%
RT site		
Brain	5	11.6%
Bone—spine	19	44.2%
Bone—pelvis	9	20.9%
Bone—other	6	14.0%
Other	4	9.3%
Delivered dose (cGy)		
Median	3000	
Range	800–4005	
Number of fractions		
Median	10	
Range	1–15	
Technique		
3D-CRT	29	67.4%
IMRT	2	4.7%
VMAT	4	9.3%
SBRT	7	16.3%
Electron	1	2.3%

Abbreviations: 3D-CRT = 3-dimensional conformal radiation therapy; IMRT = intensity modulated radiation therapy; VMAT = volumetric modulated arc therapy; SBRT = stereotactic body radiation therapy.

patient (2.3%) received electron therapy to cutaneous lesions on the breast. Median delivered RT dose and fraction were 30Gy (range 8.0–40.05Gy) and 10 fractions (range 1–15).

3.2. Safety

Non-hematologic and hematologic toxicities are presented in Tables 3 and 4. There were 5 (16.7%) and 11 (36.7%) grade 2 gastrointestinal and constitutional toxicities reported, respectively. Reported non-hematologic toxicities included dyspepsia, esophagitis, nausea, constipation, anorexia, fatigue, insomnia, and depression. No grade ≥3 constitutional, gastrointestinal, or neurologic toxicities were noted.

The most observed toxicity was hematologic toxicity. Overall, the rate of grade 2–3 hematologic toxicities was not increased after RT. There were 16 (53.3%), 3 (10.0%), and 14 (46.7%) grade 2–3 hematologic adverse events before, during, and after RT, respectively. There were 2 patients (6.7%) with grade 3 leukopenia before and after RT, and 3 patients (10.0%) with grade 3 neutropenia prior to RT. None of the patients who had grade 2–3 hematologic

Table 3
Gastrointestinal and constitutional toxicities (n = 30 patients).

	Grade 2 (n)	%	Grade ≥3 (n)	%
Gastrointestinal				
Dyspepsia	1	3.3%	0	0
Esophagitis	1	3.3%	0	0
Nausea	1	3.3%	0	0
Constipation	2	6.7%	0	0
Total	5	16.7%	0	0
Constitutional				
Anorexia	4	13.3%	0	0
Fatigue	4	13.3%	0	0
Insomnia	1	3.3%	0	0
Depression	2	6.7%	0	0
Total	11	36.7%	0	0

Table 4
Hematologic Toxicities (n = 30 patients).

	Pre RT		During RT		Post RT	
	n	%	n	%	n	%
Anemia						
Grade 2	6	20.0%	1	3.3%	2	6.7%
Grade 3	0	0%	0	0%	0	0%
Grade 4	0	0%	0	0%	0	0%
Leukopenia						
Grade 2	3	10.0%	2	6.7%	5	16.7%
Grade 3	2	6.7%	0	0%	2	6.7%
Grade 4	0	0%	0	0%	0	0%
Neutropenia						
Grade 2	2	6.7%	0	0%	5	16.7%
Grade 3	3	10.0%	0	0%	0	0%
Grade 4	0	0%	0	0%	0	0%
Thrombocytopenia						
Grade 2	0	0%	0	0%	0	0%
Grade 3	0	0%	0	0%	0	0%
Grade 4	0	0%	0	0%	0	0%
All						
Grade 2	11	36.7%	3	10.0%	12	40.0%
Grade 3	5	16.7%	0	0%	2	6.7%
Grade 4	0	0%	0	0%	0	0%

toxicities during or acutely after radiotherapy required medical intervention or dose reduction of CDK 4/6 inhibitor. No grade 4 or higher hematologic toxicities were observed. No radiation dose-response effect was observed for toxicities.

No patients had to stop CDK4/6 inhibitors or RT due to toxicity. Furthermore, no patients required dose reduction of CDK4/6 inhibitors during or after RT, although there were 4 patients who were already on a reduced dose of palbociclib prior to RT due to previous medication-related toxicity.

3.3. Clinical outcomes

At the time of the present study, 13 out of 30 patients are living. The median time from RT to last known follow-up or death is 22.3 months (range 1.0–46.8 months). All but one patient (29/30) experienced either partial (20/30) or complete (9/30) symptom relief. Local control rates were 94.4% at 6 months and 91.7% at 12 months.

4. Discussion

As CDK4/6 inhibitors are recognized as a standard of care first-line therapy for advanced HR + breast cancer, the question on safety of combined RT and CDK4/6 inhibitor use is highly relevant to clinical practice. In this study, no grade 3 or higher non-

hematologic toxicities were observed in the setting of combined CDK 4/6 inhibitor and palliative radiotherapy in patients with metastatic breast cancer. Although hematologic toxicity was most observed, the incidence was low, and the rate of grade 2–3 hematologic toxicities was not increased during or after radiotherapy. There were no grade 4–5 hematologic toxicities. No patient had to stop radiotherapy due to toxicities and every patient except one (96.7%) achieved palliation with RT.

Our findings are consistent with previous analyses assessing the safety of CDK 4/6 inhibitor and radiotherapy. Like our study, the most studied agent was palbociclib, as it was the first CDK 4/6 inhibitor to be approved. In 2017 and 2018, Hans et al. and Meattini et al. reported preliminary results in five patients each treated with palbociclib and ribociclib, respectively, combined with RT [9,10]. The two studies did not show increased toxicities with combined therapy. Subsequent studies have shown that grade ≥2 non-hematologic toxicities were rare. Grade ≥2 hematologic toxicities ranged between 13 and 31% of patients but were not increased compared to patients receiving CDK 4/6 inhibitor alone [11–14]. These findings are reassuring considering that neutropenia is the most common adverse effect associated with CDK4/6 inhibitors, and radiotherapy can also lead to decreased blood counts. In the previous clinical trials, the rates of grade ≥3 neutropenia ranged between 66 and 70% with palbociclib [1,2], 57–63% with ribociclib [3], and 21–27% with abemaciclib [4]. In our study, there was no grade 4 hematologic toxicity and the rates of grade 3 hematologic toxicities were low at 16.7%, 0%, 6.7% before, during, and after RT, without a demonstrable increase of hematologic adverse events due to RT. This result may be related to the short duration of palliative RT courses (median 10 fractions over 2 weeks) during which a complete blood count may not have been obtained. However, there was also no increase in grade 3 hematologic toxicities even after completion of radiotherapy.

On the other hand, Messer et al. highlighted a case of early radiation dermatitis resulting in skin breakdown requiring hospitalization in the setting of concurrent palbociclib and radiotherapy to a metastatic supraclavicular lymph node, after 40Gy/20 fractions out of planned 60Gy/30 fractions was delivered [16]. The patient had to stop palbociclib after 20 fractions of RT and finished the remaining 10 fractions without concurrent palbociclib. One explanation for the severe toxicity in this patient could be that the irradiated volume and dose were higher than the usual palliative RT regimens used in the aforementioned studies. In our cohort, no grade ≥2 radiation dermatitis was observed. Kawamoto et al. reported a patient with severe acute radiation-induced enterocolitis after completion of pelvic palliative RT with 30Gy in 10 fractions with concurrent palbociclib [15]. In our study, we did not observe any severe acute gastrointestinal toxicity even with pelvic RT (n = 9, 20.9%). In addition, David et al. detailed a case series in which a patient died of grade 5 pneumonitis after palliative radiotherapy with 20 Gy in 5 fractions to symptomatic mediastinal nodal metastases [18]. The patient was newly started on palbociclib four months after RT and rapidly developed progressive shortness of breath one week later. The authors postulated that this was due to radiation recall, given that the area of pneumonitis was localized to the high RT dose region. High daily RT dose has been associated with increased risk of radiation pneumonitis and it is possible that this patient's high dose per fraction contributed to the incidence of fatal pneumonitis [20]. In our study, only one patient received mediastinal RT (30 Gy in 10 fractions) with treatment volume overlapping with the lungs. This patient experienced grade 2 esophagitis during RT but no pulmonary toxicities.

Although clinical studies have shown overall acceptable toxicity for combined CDK4/6 inhibitor and radiotherapy, the underlying mechanisms of combined therapy are still being understood.

Preclinical studies have demonstrated the radiosensitization effects of CDK4/6 inhibitors in cancer cells via inhibition of retinoblastoma protein phosphorylation leading to cell cycle arrest, inhibiting DNA damage repair, enhancing apoptosis, and inducing cellular senescence [8,21–24]. Recent discovery suggests that CDK4/6 inhibitors also protect normal tissue cells by inducing protective DNA damage repair and promoting anti-tumor immunity, but they do not protect tumor cells from radiation [25–27]. In vivo studies by Wei et al. and Lee et al. showed that palbociclib use before a single fraction radiotherapy protected mice against acute gastrointestinal radiation syndrome in mice [28,29]. Surprisingly, however, Lee et al. also found that palbociclib treatment before and during treatment with five daily fractions of RT exacerbated acute gastrointestinal radiation syndrome [27]. These findings suggest that, although transient inhibition of cell proliferation via CDK4/6 inhibition may improve the survival of the intestinal crypt cells, prolonged CDK4/6 inhibition may impair the regeneration of normal healthy cells. Although mounting evidence shows that CDK4/6 inhibition simultaneously prevents tumor growth and protects normal tissue against treatment-related toxicities, there is clearly more to be elucidated on the mechanisms of combined CDK4/6 inhibition and radiotherapy. Another consideration is the pharmacokinetics of CDK4/6 inhibitors. The half-life of palbociclib is 29 h, meaning that 90% of it will be eliminated after approximately 4 days (3.3 half-lives), and 94–97% after 4.8–6 days (4–5 half-lives). Taken together, a reasonable approach would be to administer CDK4/6 inhibitors and radiotherapy concurrently, or conservatively, hold the CDK4/6 inhibitor use for 4–6 days prior to radiotherapy.

This study has limitations that are inherent to the retrospective study design. This includes missing data such as adverse events that may not have been documented. Missing data may include laboratory values like blood counts, which are not routinely captured during radiotherapy, especially during short treatment courses. To our knowledge, there are only a handful of retrospective studies on safety and efficacy of concomitant CDK 4/6 inhibitor use and RT in patients with metastatic breast cancer. This study contained one of the largest number of patients and treated sites compared to prior studies. Moreover, a major strength of this study is that the CDK 4/6 inhibitors' half-lives were considered and the time between CDK 4/6 inhibitor use and RT was limited to maximum 14 days (median 3.5 days) to maintain clinical relevance.

We await prospective clinical data on combined CDK 4/6 inhibitor and RT use. The phase II ASPIRE trial (NCT03691493) is assessing the response and toxicities of RT to bone metastases with concurrent palbociclib and hormone therapy in patients with metastatic breast cancer. Similarly, the phase II CLEAR trial (NCT03750396) is investigating the role of metastasis-directed local therapies including stereotactic RT combined with endocrine and/or concurrent CDK4/6 inhibitors for oligometastatic breast cancer. The PALATINE trial (NCT03870919) examines locoregional treatment of the primary breast tumor with surgery and/or radiotherapy in addition to hormonal and concurrent palbociclib therapy for de novo metastatic breast cancer.

5. Conclusion

In summary, our study demonstrates overall limited toxicities and high response rates after combined CDK 4/6 inhibitor and palliative radiotherapy in patients with metastatic breast cancer. The results of ongoing prospective clinical trials should further elucidate the safety and efficacy of combined CDK 4/6 inhibitor and radiotherapy.

Declaration of competing interest

The authors have no conflict of interest to declare.

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