



Original article

Concurrent radiotherapy with palbociclib or ribociclib for metastatic breast cancer patients: Preliminary assessment of toxicity



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ABSTRACT

Objective: To evaluate the early toxicity of concurrent use of radiotherapy in association with CDK4/6 inhibitors (palbociclib or ribociclib) in patients with hormone-receptors positive metastatic breast cancer.

Material and methods: Records of patients with histologically proven metastatic or locally advanced breast cancer treated in our institution were reviewed. Patients who received radiotherapy and concurrent palbociclib or ribociclib were selected. Toxicity was assessed according to the National Cancer Institute Common Terminology Criteria for Adverse Events version 4.0 (NCI-CTCAE V4.0).

Results: Sixteen consecutive metastatic breast cancer patients with 24 radiotherapy treatments were studied. Thirteen patients (81.3%) received palbociclib, 3 (18.7%) patients received ribociclib concurrently with RT (18 and 5 radiotherapy courses respectively). The majority of patients (68.7%) received palliative radiotherapy to the bones (median dose 30 Gy, range 8–36 Gy). Five patients (31.2%) were treated in oligo-metastatic or oligo-progressive sites of disease with higher doses (median dose = 50 Gy, range 39.6–60 Gy). The most common toxicity observed was hematological toxicity. Neutropenia was common (grade 2 = 12.5%; grade 3 = 25%, grade 4 = 6.3%); 60% of patients experiencing grade ≥ 3 neutropenia had already experienced neutropenia during previous cycles of palbociclib. One patient (6.3%) completed the RT course earlier (48 Gy of 50 Gy prescribed) and another patient (6.3%) suspended RT for 2 days.

Conclusion: concomitant treatment of CDK4/6 and radiotherapy seems well tolerated; high grade hematological toxicity is common, but did not change treatment course in the majority of patients. Previous toxicity should be carefully evaluated as it usually reoccurs.

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1. Introduction

Selective inhibitors of cyclin-dependent kinase (CDK) 4 and 6 have recently been introduced in clinical practice for treatment of metastatic hormone receptors positive (HR+) breast cancer patients. CDK 4/6 inhibitors given concurrently with anti-estrogen therapy with selective estrogen receptor modulators and/or selective estrogen receptor degraders have led to substantial progression free survival (PFS) improvements in the first and second line settings [1–5]. To date, three CDK4/6 inhibitors are approved by the US Food and Drug Administration (FDA) and by the European

Medicines Agency (EMA), including: palbociclib, ribociclib and abemaciclib. Abemaciclib has only recently been approved in Europe by the EMA.

This class of agents does not kill cells directly, but arrests the cell cycle during the restriction point when the cell passes from G1 to S phase going through another cell division putting them into senescence. This may represent a mechanism potential of cell radio sensitisation as during S phase cells are more radioresistant. However, there is limited published data regarding the combination of these agents and radiotherapy in preclinical models. Palbociclib in combination with radiation therapy (RT) on glioblastoma (GBM) patient-derived cell lines (PDCLs; RB1 retained; CDKN2A loss) resulted in a significant increase of apoptotic cell death and impediment of colony formation [6].

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Abemaciclib enhanced the radio-sensitivity of NSCLC cells independent of RAS or EGFR status in cell lines with functional p53 and RB protein [7]. Moreover, in a murine model, palbociclib before a single dose of subtotal body irradiation seemed to protect from gastrointestinal acute radiation syndrome (GI-ARS); on the contrary, treatment with palbociclib before and during 5 daily fractions of subtotal body irradiation exacerbated GI-ARS [8].

While the three CDK4/6 inhibitors are more likely to have similar efficacy, the toxicity profiles are different. Palbociclib and ribociclib have dose limiting toxicity of neutropenia, while the dose limiting toxicity for abemaciclib is diarrhea and may be related to its greater affinity for CDK4 over CDK6. Many patients undergoing therapy with these agents will require palliative radiotherapy. However, radiotherapy involving bone marrow or delivering dose to the gastrointestinal (GI) tract may represent additional risk factors for myelo-suppression and GI toxicity [9].

Despite preliminary reports of palbociclib [10] and ribociclib [11] with concomitant palliative radiotherapy suggested encouraging results and safety, recently a case of severe acute radiation-induced enterocolitis after combined palbociclib and palliative radiotherapy treatment was reported [12].

Based on the above considerations the aim of this study was to evaluate the early toxicity of concurrent use of radiotherapy, palbociclib or ribociclib in patients with HR-positive metastatic breast cancer.

2. Material and Methods

2.1. Study group

We reviewed the records of patients with histologically proven metastatic or locally advanced breast cancer treated in our institution from January 2017 to June 2018 in a clinical practice setting. Patients who received external beam radiotherapy to bone metastases or extra-bone/nodal relapse areas and concurrent CDK 4/6 inhibitors (palbociclib or ribociclib) were selected for this study. All patients had signed an informed consent for the use of their data for research purposes.

2.2. Treatment

Palbociclib was given at the dose of 125 mg per day for 3 weeks on, one week off. Some patients received a reduced dose of 100 mg per day in case of reported former toxicity. The dose was given in combination with letrozole in first line treatment or fulvestrant in women with disease progression following endocrine therapy. Premenopausal patients also received Ovarian Function Suppression (OFS) by Luteinizing Hormone-Releasing Hormone-agonists (LHRH-agonists).

Ribociclib was given at the dose of 600 mg per day for 3 weeks on, one week off in combination with letrozole.

3D conformal radiotherapy technique (3D-CRT) with moderate hypofractionation was used for the majority of treatments to bone metastases. In some patients with oligometastatic bone disease or extra-bone site of disease, intensity modulated radiotherapy (IMRT) or volumetric modulated arc therapy (VMAT) was carried out.

2.3. Statistics

General descriptive statistical calculations were done on the current baseline and on treatment clinical parameters. Continuous variables were summarized with median and range, whereas counts and percentages were used to summarize categorical variables.

Toxicity was assessed according to the National Cancer Institute Common Terminology Criteria for Adverse Events version 4.0 (NCI-CTCAE V4.0). A Numerical Rating Scale (NRS) was used to assess pain intensity before and after RT treatment. Response evaluation was in line with Response Evaluation Criteria in Solid Tumors 1.1 (RECIST 1.1).

3. Results

3.1. Study population

Sixteen consecutive metastatic breast cancer patients with 24 radiotherapy treatments were studied. The distribution of baseline patients' characteristics is shown in Table 1. Median age was 54 years (range 30–80). The majority of patients had metastatic disease at diagnosis (56.3%) and had not previously received endocrine therapy for metastatic disease (81.3%). Thirteen patients (81.3%) received palbociclib, 3 (18.7%) patients received ribociclib concurrently with RT (19 and 5 radiotherapy courses respectively). Six patients started treatment with CDK4/6 inhibitors concurrently with RT, while 10 patients (62.5%) were already receiving cyclin inhibitors at the time of RT (mean time of treatment = 3 months, range 1–8).

3.2. Radiotherapy treatments

Radiotherapy treatments details are summarized in Table 2. Five patients (20.8%) received more than one radiotherapy course (median = 2, range = 2–4). Most patients (68.7%) received palliative radiotherapy to the bones (median dose 30 Gy, range 8–36 Gy). Five patients (31.2%) were treated to oligometastatic (n = 3, 18.7%) or oligo-progressive (n = 2, 12.5%) sites of disease with higher doses (median dose = 50 Gy, range 39.6–60 Gy). Three of these latter patients were treated on bone sites of disease (sternum, dorsal spine, humeral head), one patient (6.2%) was treated on chest wall for skin metastases, one (6.2%) to a nodal site of relapse (internal mammary chain). One patient (6.25%) received stereotactic fractionated radiotherapy to a lesion of the humeral head (total dose = 21 Gy; fraction dose = 7 Gy). 3D-CRT with multiple field was used for the majority of treatment (79.2%); IMRT or VMAT were

Table 1
Patients' characteristics.

Total, N (%)	16 (100%)
Age	Median 54 Range 30-80
Histology	
Ductal carcinoma	13 (81.3%)
Lobular carcinoma	2 (12.4%)
Others	1 (6.3%)
Menopause Status	
Pre-perimenopausal	8 (50%)
Post menopausal	8 (50%)
Metastatic disease	
At diagnosis	9 (56.3%)
Relapse after local treatment	7 (43.7%)
Previous line of endocrine therapy for metastatic disease	
Yes	3 (18.7%)
Not	13 (81.3%)
Previous chemotherapy for metastatic disease	
Yes	2 (12.4%)
Not	14 (87.6%)
Site of metastases	
Bone	14 (87.4%)
Chest wall	1 (6.3%)
Nodal	1 (6.3%)

Table 2
Radiotherapy treatment details.

Total treatments = 24 (100%)		
Site		
Bone = 22 (91.6%)	Spine = 8 (33.3%)	PRESCRIBED DOSE (total dose, Gy/dose per fraction, Gy = number of treatments)
	Thorax = 4 (16.6%)	30/3 = 2; 36/3 = 1; 39.6/2.2 = 1
	Abdomen = 4 (16.6%)	30/3 = 3; 8/8 = 1
	Non spine = 14 (58.3%)	20/4 = 3; 30/3 = 3; 21/7 = 1; 50/2 = 1
	Thorax = 8 (37.5%)	20/4 = 3; 30/3 = 3
	Pelvis = 6 (25.0%)	
Chestwall = 1 (4.2%)	Skin metastases	50/2
Nodal = 1 (4.2%)	Internal mammary nodal relapse	60/2
Radiotherapy technique		
3D-CRT = 19 (79.2%)		
IMRT = 2 (8.3%)		
VMAT = 3 (12.5%)		
CONCURRENT CDK4/6 INHIBITOR		
Palbociclib = 19 (79.2%)		
Ribociclib = 5 (20.8%)		

used in five cases (20.8%).

3.3. Safety

Safety data is shown on [Table 3](#). The most common toxicity observed was hematological toxicity. Neutropenia was common (grade 2 = 12.5%; grade 3 = 25%, grade 4 = 6.3%). In all patients but two, the rate of bone marrow treated was limited (<5%). One out of three patients undergoing concurrent treatment with ribociclib experienced grade 2 neutropenia with no other toxicity. Among patients receiving concurrent palbociclib, one patient (6.3%) suspended RT for 7 days and thereafter completed the RT course earlier (48 Gy of 50 Gy prescribed) and another patient (6.3%) suspended RT for 2 days. Three out of five patients treated with concurrent palbociclib experiencing grade ≥ 3 neutropenia (60%) had already experienced neutropenia during previous cycles of palbociclib. Three patients developed grade 3 neutropenia at the end of radiotherapy treatment (day 16, 18 and 21 from the start of palbociclib) thus they did not suspend the RT course. In these patients, neutropenia spontaneously improved with CDK4/6 suspension during the week off of treatment. Only one patient needed one additional week of suspension from palbociclib prior to restarting

treatment. The dose of palbociclib was reduced in a patient who developed grade 4 neutropenia. This latter patient, who started palbociclib with radiotherapy (to chest wall for skin metastases), was heavily pretreated as she had received neoadjuvant chemotherapy a few months previously. One patient (6.3%) suspended palbociclib at mid-course RT (day 17 from the start of palbociclib) with regression of grade 3 neutropenia to grade 2. This patient restarted palbociclib after the planned week off at the same dosage. Treatment details of patients experiencing grade ≥ 3 neutropenia are given in [Table 4](#).

Two patients (12.5%) experienced grade 1 fatigue and one patient (6.3%), treated on chest wall for skin metastases, had grade 2 skin ulceration. Adverse events during the following cycle of CDK 4/6 inhibitors were not substantially different (see [Table 3](#)).

3.4. Clinical outcomes

At the time of the present study, all patients are still on treatment with CDK4/6 inhibitors. With a median follow-up of 6.3 months (range = 2.3–16.9 months), all patients treated for bone metastases achieved pain relief (NRS pre-RT = 5.29; SD = 2.7; NRS post RT = 2.1; SD = 2.5; $p < 0.001$). In patients treated for oligo-

Table 3
Adverse Events description.

Type of Adverse Event	During CDK4/6 inhibitor cycle delivered concurrently with RT	During following CDK4/6 inhibitor cycle
Hematological		
Neutropenia		
Grade 1	0 (0.0%)	0 (0.0%)
Grade 2	2 (12.5%)	1 (6.3%)
Grade 3	4 (25.0%)	4 (25.0%)
Grade 4	1 (6.3%)	0 (0.0%)
Trombocytopenia		
Grade 1	2 (12.5%)	0 (0.0%)
Grade 2	0 (0.0%)	0 (0.0%)
Grade 3	0 (0.0%)	0 (0.0%)
Grade 4	0 (0.0%)	0 (0.0%)
Anemia		
Grade 1	3 (18.8%)	2 (12.5%)
Grade 2	0 (0.0%)	0 (0.0%)
Grade 3	0 (0.0%)	0 (0.0%)
Grade 4	0 (0.0%)	0 (0.0%)
Non Hematological		
Fatigue		
Grade 1	2 (12.5%)	2 (12.5%)
Grade >2	0 (0.0%)	0 (0.0%)
Skin		
Grade 1	1 (6.3%)	0 (0.0%)
Grade >2	1 (6.3%)	0 (0.0%)

Table 4
Patients with grade ≥ 3 toxicity: treatment details.

Patient	Age	CDK4/6 inhibitor	Mean time (months) of treatment with CDK4/6 inhibitors (before RT)	Previous toxicity (grade/type)	Toxicity during RT (grade/type)	Toxicity after RT (following cycle)	RT volume	RT dose (Gy/Fx)	RT technique	RT suspension (days)
1	44	Palbociclib 100 mg	1	Febrile neutropenia Grade 1 Anemia	Grade 3 neutropenia	Grade 3 neutropenia	Humeral head	30/3	3D-CRT	0
2	53	Palbociclib 125 mg	1	Grade 3 neutropenia	Grade 3 neutropenia	Grade 3 neutropenia	Lumbar spine (L3)	30/3	3D-CRT	0
3	39	Palbociclib 125 mg	0	–	Grade 4 neutropenia	Grade 3 neutropenia	Chest wall	48/2	VMAT	7 ^a
4	76	Palbociclib 125 mg	3	Grade 3 neutropenia	Grade 3 neutropenia	Grade 2 neutropenia	Left femoral neck	30/3	3D-CRT	0
5	43	Palbociclib 125 mg	0	–	Grade 3 neutropenia	Grade 2 neutropenia	Scapula	20/4	3D-CRT	0

^a RT closed earlier: planned dose 50Gy, delivered dose 48 Gy.

metastatic oligo-progressive disease, we observed 2 complete responses (patients with extra-bone disease), 2 partial responses and 1 stable disease in patients with bone metastases.

4. Discussion

With the recent introduction of CDK4/6 inhibitors in the management of metastatic HR + breast cancer patients, we aimed to explore the feasibility of the combination of CDK4/6 inhibitors with radiotherapy treatments. We reported safety data on 24 radiotherapy treatments performed in a population of non-selected consecutive patients treated with palbociclib (81.3%) or ribociclib (18.7%) showing limited and manageable toxicity.

The most common adverse event was neutropenia observed in 7/16 (43.7%) patients with a rate of grade ≥ 3 toxicity of 31.3%. No other relevant toxicity was developed. The toxicity observed is consistent with published safety data of patients treated with CDK4/6 inhibitors. A recent meta-analysis, exploring the incidence of hematological adverse effects in patients treated with CDK4/6 inhibitors, reported a grade 3–4 neutropenia ranging from 21.1 to 66% with a median time to any grade of neutropenia ranging between 15 and 20 days and a median duration of neutropenia ranging from 7 to 8 days [13].

An interest finding of our study was that in patients who developed high grade neutropenia (≥ 3) in previous cycles of CDK4/6 inhibitor therapy, and subsequently underwent radiotherapy, we did not observe a deteriorating trend of neutropenia during radiotherapy. Thus, radiotherapy does not seem to represent an additional myelo-suppressive factor for these patients. Also radiotherapy given during the CDK 4/6 week off did not worsen toxicity. On the other hand, clinicians should carefully evaluate and monitor these patients during radiotherapy course as hematological toxicity is likely to occur again.

In our series, only 3/16 patients (18.7%) underwent treatment changes due to an adverse event: one patient completed radiotherapy course earlier, one patient suspended RT for 2 days and one patient suspended palbociclib during RT after 17 days from the beginning of the cycle. Moreover, in all patients but one who developed grade 3/4 neutropenia, subsequent dosage of palbociclib was not reduced as they recovered quickly from neutropenia. This was particularly important as it enabled us to perform RT in a palliative setting without interruption, thereby not compromising efficacy. In fact, all patients treated for bone metastases achieved pain relief and patients treated for oligo-metastatic oligo-progressive disease had good clinical responses (2 complete responses, 2 partial responses and 1 stable disease).

Two very first preliminary reports were published on concurrent treatment of RT with palbociclib [10] and ribociclib [11]. Hans S et al. reported the outcome of 5 metastatic breast cancer patients treated with palliative RT in association with Palbociclib and Fulvestrant. All patients experienced symptom control with an RT dose of 20 Gy delivered in five fractions; one patient treated for liver metastases with radiosurgery achieved disease stability in the site treated. Grade 3 neutropenia was observed in 2 patients, grade 3 anemia in 1 case a grade 3 thrombopenia. Two patients also presented grade $\frac{1}{2}$ mucositis [10]. In the other report, Meattini et al. described data regarding the combination of ribociclib and palliative RT on the first five patients treated at their institution. In this small series, patients were treated to a total dose of 20/30 Gy given in 5 fractions, 2 out of 5 patients developed grade 3–4 toxicity, one hematological (neutropenia), one gastrointestinal (diarrhea/vomiting). Radiotherapy was never suspended, while ribociclib suspension was needed in 2 cases [11].

Given these safety results, our data seems to confirm on a larger series, including also longer radiotherapy treatment, the feasibility of the concomitant treatment without additional toxicity.

Recently a case of severe acute radiation induced enterocolitis after concurrent treatment of palbociclib and radiotherapy to the left iliac bone and first sacral vertebrae was reported [12]. The patient started palliative radiotherapy to pelvis bones 3 months after the beginning of therapy with Palbociclib 100 mg and Fulvestrant. During RT (30 Gy delivered in 10 fractions) she developed grade 1 diarrhea and after 3 days she experienced a symptoms worsening with abdominal pain, bloating and bloody diarrhea (diagnosed as grade 3 colitis). A CT scan showed colon wall thickening corresponding to the irradiation field and colonoscopy revealed erosion and angiectasis of the descending colon. The authors concluded that the radiation induced colitis might be explained with an over-sensitisation secondary to palbociclib administration.

In our series we did not observe any gastrointestinal toxicity neither in pelvis ($n = 6$, 26%), nor in abdomen ($n = 4$, 17.4%) treatments, with 6 treatments delivering a dose of 30 Gy given in 10 fractions (as in the case report). This may be due to the use of high conformal multiple fields 3D-technique used in most of cases, even in palliative setting.

A recent meta-analysis investigating gastrointestinal effects of CK4/6 inhibitors in breast cancer patients reported an incidence of all grade diarrhea of 19.1–35% and of high grade diarrhea of 0–4% [14]. Therefore it is reasonable that high grade GI toxicity during and shortly after radiotherapy is possible but not common. It should be noted that the patient who developed the severe case of

radiation induced colitis [12] had already developed G1 diarrhea before radiotherapy after the start of treatment with palbociclib. Consequently, patients who have already had GI toxicity on CDK4/6 inhibitors treatment should be carefully evaluated and given high conformal treatment with greatest GI mucosa sparing.

In conclusion the concomitant treatment of CDK4/6 and radiotherapy seem to be well tolerated especially in palliative setting; high grade hematological toxicity is common, but did not change treatment course in most of the patients. Previous toxicity should be carefully evaluated as it usually reoccurs.

Conflicts of interest

None.

Ethical approval

Not required.

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