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Research Letter

Safety and Efficacy of Palbociclib and Radiation Therapy in Patients With Metastatic Breast Cancer: Initial Results of a Novel Combination

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Abstract

Purpose: Palbociclib is a selective cyclin-dependent kinase 4/6 inhibitor approved for metastatic ER+/HER2- breast cancer. Preclinical evidence suggests a possible synergistic effect of palbociclib when combined with radiation therapy (RT); however, the toxicity of this pairing is unknown. We report preliminary results on the use of this combination.

Methods and Materials: Records of patients treated with palbociclib at our institution from 2015 to 2018 were retrospectively reviewed. Patients who received RT for symptomatic metastases concurrently or within 14 days of palbociclib were included. Local treatment effect was assessed by clinical examination and subsequent computed tomography/magnetic resonance imaging. Toxicity was graded based on Common Terminology Criteria for Adverse Events version 5.0.

Results: A total of 16 women received palliative RT in close temporal proximity to palbociclib administration. Four patients received palbociclib before RT (25.0%), 5 concurrently (31.3%), and 7 after RT (43.8%). The median interval from closest palbociclib use to RT was 5 days (range, 0-14). The following sites were irradiated in decreasing order of frequency: bone (11 axial skeleton [9 vertebra and 2 other]; 4 pelvis; 3 extremity), brain (4: 3 whole brain RT and 1 stereotactic radiosurgery), and mediastinum (1). The median and mean follow-up time is 14.7 and 17.6 months (range, 1.7-38.2). Pain relief was achieved in all patients. No radiographic local failure was noted in the 13 patients with evaluable follow-up imaging. Leukopenia, neutropenia, and thrombocytopenia were seen in 4 (25.0%), 5 (31.3%), and 1 (6.3%) patient before RT. After RT, 5 (31.3%), 1 (6.3%), and 3 (18.8%) patients were leukopenic, neutropenic, and thrombocytopenic, respectively. All but 2 (grade 2) hematologic toxicities were grade 1.

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No acute or late grade 2+ cutaneous, neurologic, or gastrointestinal toxicities were noted. Toxicity results did not differ based on disease site, palbociclib-RT temporal association, or irradiated site.
Conclusions: The use of RT in patients receiving palbociclib resulted in minimal grade 2 and no grade 3+ toxicities. This preliminary work suggests that symptomatic patients receiving palbociclib may be safely irradiated.

Introduction

Palbociclib is a selective cyclin-dependent kinase (CDK) 4/6 inhibitor approved for the treatment of metastatic ER+/HER2- breast cancer.[1-3] The interaction of cyclin D with CDK4 and CDK6 results in the hyperphosphorylation of the retinoblastoma gene product, which ultimately leads to progression from G1 to the S phase of the cell cycle.[4] Palbociclib-induced inhibition of CDK4/6 prevents cell cycle progression and thus halts uncontrolled cancer cell division.

Preclinical data suggest palbociclib may augment the therapeutic effect of radiation therapy (RT) via multiple methods.[5-7] Despite this potential benefit, clinicians seldom use this combination out of fear that RT may exacerbate palbociclib toxicity, particularly neutropenia and leukopenia. We report the preliminary results of patients who received RT while being treated with palbociclib for metastatic breast cancer.

Methods and Materials

With institutional review board approval, we retrospectively reviewed records of all patients who were treated with palbociclib at Rush University Medical Center from 2015 to 2018. The starting palbociclib dose was 125 mg daily from day 1 to 21 in association with either fulvestrant 500 mg every 28 days or letrozole 2.5 mg daily. Patients who received RT for symptomatic metastasis concurrently or within 14 days of palbociclib administration (mean half-life of 26 hours[8]) were included in our analysis.

Patient charts were reviewed for the following baseline patient and treatment characteristics: age, sex, Eastern Cooperative Oncology Group performance status, laboratory values, treatment site, RT technique (3-dimensional conformal RT, intensity modulated RT, whole brain radiation therapy [WBRT], fractionated stereotactic radiosurgery [fSRS], stereotactic body RT) and radiation dose/fractionation.

Pain relief was assessed by the patient's self-rated pain scores (range, 0 [no pain] to 10 [worst pain ever]). Local treatment effect was determined by subsequent computed tomography or magnetic resonance imaging, if applicable. Toxicity was graded based on National Cancer Institute Common Terminology Criteria for Adverse Events version 5.0 during the weekly clinic and follow-up visits in the radiation or medical oncology departments.

Results

Patient and treatment characteristics

A total of 16 women (median age, 59.6 [range, 33.3-91.0] years) received palliative RT in close temporal association with palbociclib (Table 1). The median duration of palbociclib use was 15.7 months (1.9-38.0). The median time of closest palbociclib use to RT administration was 5 days (range, 0-14): 4 patients received palbociclib before RT (25.0%), 5 (31.3%) concurrently, and 7 (43.8%) after RT.

The following sites were treated in order of frequency: bone (11 axial skeleton [9 vertebra; 2 other]; 4 pelvis; 3 extremity), brain (4: 3 WBRT and 1 fSRS), and mediastinum (1). Sixteen of 18 osseous sites received conventional RT (range, 30-37.5 Gy/10-15 fractions fxn),

Table 1 Baseline patient characteristics

Parameters	n (range) or median (range)
Prior breast RT	8 (50%)
Prior chemotherapy	8 (50%)
Prior hormone therapy	10 (62.5%)
Age at RT, y	59.6 (33.3-91.0)
Palbociclib +	
Fulvestrant	6 (37.5%)
Letrozole	10 (62.5%)
Closest palbociclib to RT interval (d)	5 (0-14)
Closest palbociclib proximity to RT	
Prior	4 (25.0%)
Concurrent	5 (31.3%)
Post	7 (43.8%)
RT site	
Bone: axial skeleton (vertebra)	9 (39.1%)
Bone: axial skeleton (other)	2 (8.7%)
Bone: pelvis	4 (17.4%)
Bone: extremity	3 (13.0%)
Brain	4 (17.4%)
Mediastinum	1 (4.3%)

Abbreviation: RT = radiation therapy.

Table 2 RT treatment characteristics

Patient	RT site	RT technique	RT dose/fxn	Pain relief	LR
1	C2	SBRT	18 Gy/1 fxn	Yes	No
2	Left iliac crest	SBRT	30 Gy/3 fxn	Yes	No
3	C2-C7	3D-CRT	30 Gy/10 fxn	Yes	No
4	Right shoulder	3D-CRT	30 Gy/10 fxn	Yes	No
	Bilateral knees	3D-CRT	30 Gy/10 fxn		No
5	T12-L2	3D-CRT	30 Gy/10 fxn	Yes	No
	Left hip	3D-CRT	30 Gy/10 fxn		No
6	T8-L1	3D-CRT	35 Gy/14 fxn	Yes	No
7	T6-8	3D-CRT	35 Gy/14 fxn	Yes	No
	Right calvarium	IMRT	37.5 Gy/15 fxn		No
8	L3-sacrum	3D-CRT	35 Gy/14 fxn	Yes	No
	Right hip	3D-CRT	35 Gy/14 fxn		No
	Left ribs	3D-CRT	35 Gy/14 fxn		No
9	L-S spine	3D-CRT	35 Gy/14 fxn	Yes	No
	Right hemipelvis	3D-CRT	35 Gy/14 fxn		No
	Right proximal femur	3D-CRT	35 Gy/14 fxn		No
10	L3-sacrum	3D-CRT	30 Gy/10 fxn	Yes	No
11	T10-T12	3D-CRT	30 Gy/10 fxn	Yes	No
12	Left frontal cavity	fSRS	25 Gy/5 fxn	-	No
13	Brain	WBRT	30 Gy/10 fxn	-	No
14	Brain	WBRT	35 Gy/14 fxn	-	-
15	Brain	WBRT	30 Gy/10 fxn	-	-
16	Mediastinum	IMRT	36 Gy/18 fxn	Yes	No

Abbreviations: 3D-CRT = 3-dimensional conformal radiation therapy; C = cervical; fSRS = fractionated stereotactic radiosurgery; Fxn = fraction; IMRT = intensity modulated radiation therapy; L = lumbar; LR = local recurrence; RT = radiation therapy; SBRT = stereotactic body radiation therapy; T = thoracic; WBRT = whole brain radiation therapy.

whereas 2 received stereotactic body RT (18 Gy/1 fxn and 30 Gy/3 fxn). For brain, WBRT ranged from 30 to 35 Gy in 10 to 14 fxn and fSRS brain dose was 25 Gy in 5 fxn. The patient treated to the mediastinum received 36 Gy in 18 fxn. Table 2 shows full RT treatment characteristics for each patient.

Treatment outcomes and toxicity

At the most recent follow-up, 12 patients are still living. The median and mean time from RT to last known follow-up or death is 14.7 and 17.6 months (range, 1.7-38.2), respectively. Median pre-RT pain was 8 (range, 6-10). Pain relief was achieved in all patients (median: 2 [range, 0-3]). No radiographic local failure was noted in the 13 patients with evaluable follow-up imaging.

The combination of RT and palbociclib was well-tolerated. Grade 1 fatigue, dermatitis, and nausea were noted in 5, 3, and 1 patient, respectively. One patient who underwent WBRT developed grade 1 headache. No acute or late grade 2 or higher cutaneous, neurologic, or gastrointestinal toxicities were noted.

Table 3 shows hematologic parameters before and after RT. The median time interval from blood draw and RT was 12 days (0-40) and 8 days (1-47) for pre- and postvalues, respectively. The median pre- and post-RT white blood cell (normal, 4.0-10.0 k/uL), neutrophil (normal, 1.84-7.8 K/uL), and platelet count (normal, 150-399 K/uL) was 5.12 and 4.8, 2.83 and 3.19, and 250 and 210, respectively. Leukopenia, neutropenia, and thrombocytopenia were seen in 4 (25.0%), 5 (31.3%), and 1 (6.3%) patients before RT. After RT, 5 (31.3%; 4 new [3 grade 1 and 1 grade 2]), 1 (6.3%; grade 2), and 3 (18.8%; grade 1) patients were leukopenic, neutropenic, and thrombocytopenic, respectively.

No patients developed infections after RT. All but 2 (grade 2) hematologic toxicities were grade 1. There was no difference in toxicities based on palbociclib-RT sequencing or by irradiated site.

Discussion

Palbociclib is the first CDK 4/6 inhibitor approved for metastatic ER+/HER2- breast cancer based on the promising results of the PALOMA studies. Preclinical evidence suggests that palbociclib may act synergistically with RT. Palbociclib-induced inhibition of CDK4/6 prevents cell cycle progression to the more radioresistant S phase. Moreover, palbociclib can act as a DNA double-strand break repair inhibitor,[7] thus amplifying the anticancer effect of RT.

The most frequently seen toxicity with palbociclib is hematologic, which can also occur after irradiation. Many patients with metastatic breast cancer become

Table 3 Hematologic parameters before and after RT in patients receiving palbociclib

Patient	Irradiated Site(s)	Palbo-RT relation	Hematologic parameters*											
			Pre-RT						Post-RT					
			WBC count	Leukopenia	Neutrophil count	Neutropenia	Platelet count	Thrombocytopenia	WBC count	Leukopenia	Neutrophil count	Neutropenia	Platelet count	Thrombocytopenia
1	Axial	Post	7.24	No	5.02	No	404	No	5.10	No	2.26	No	375	No
2	Pelvis	C	5.78	No	3.34	No	247	No	5.23	No	3.25	No	247	No
3	Axial	Pre	3.05	Yes	1.07	Yes	139	Yes	4.74	No	3.19	No	193	No
4	Extremity	Post	1.72	Yes	0.76	Yes	198	No	1.35	Yes	2.46	No	167	No
5	Axial + pelvis	Post	2.66	Yes	1.07	Yes	181	No	5.14	No	3.78	No	210	No
6	Axial	C	4.13	No	2.64	No	334	No	4.80	No	3.29	No	313	No
7	Axial	Pre	8.91	No	4.86	No	420	No	7.73	No	6.08	No	165	No
8	Axial + pelvis	C	4.83	No	3.22	No	262	No	2.20	Yes	1.28	Yes	120	Yes
9	Axial + pelvis + extremity	Post	8.74	No	5.09	No	255	No	4.82	No	3.20	No	226	No
10	Axial	Pre	6.30	No	3.62	No	196	No	9.20	No	6.90	No	139	Yes
11	Axial	Post	3.26	No	1.09	Yes	181	No	3.32	Yes	1.93	No	216	No
12	Brain	C	5.30	No	3.30	No	175	No	4.46	No	2.14	No	259	No
13	Brain	Post	5.51	No	2.81	No	350	No	9.31	No	6.69	No	172	No
14	Brain	Post	5.58	No	2.84	No	475	No	3.12	Yes	2.04	No	119	Yes
15	Brain	Pre	3.60	Yes	1.42	Yes	195	No	-	-	-	-	-	-
16	Mediastinum	C	4.94	No	2.72	No	253	No	3.88	Yes	2.78	No	211	No

Abbreviations: C = concurrent with RT; Palbo = palbociclib; RT = radiation therapy; WBC = white blood cell.

* WBC, neutrophil, and platelet count measured in K/uL. Normal WBC range: 4.00-10.00 K/uL. Normal neutrophil range: 1.84-7.80 K/uL. Normal platelet range: 150-399 K/uL.

symptomatic and need RT; however, the lack of published clinical toxicity data results in physician reluctance to administer RT to patients receiving palbociclib.

Therefore, we examined the safety and efficacy of concomitant palbociclib and RT in 16 patients with breast cancer with symptomatic metastases. With a median follow-up time of 14.7 months, we report no significant increase in acute or late toxicities, particularly hematologic, with this novel combination as compared to reports of palbociclib alone. Additionally, no differences were seen when assessing toxicity based on irradiated site (axial vs pelvis vs other) or palbociclib-RT relation (pre-, post-, and concurrent; Table 3). Sustained pain relief was achieved in all patients, and no local failures were seen in the evaluable patients.

After exhaustive literature review, we found only 1 published study investigating this combination in humans. Consistent with our findings, Hans et al[9] also report no increase in toxicity in 5 patients treated with palbociclib and RT; however, their study does not report follow-up time, local control, or toxicities grouped by irradiated site or proximity of RT and palbociclib administration.

Preclinical studies of palbociclib and RT in nonbreast cancer also seem to be promising. Two studies[6,10] of palbociclib and RT in glioblastoma cell lines showed increased tumor cell apoptosis with the combination compared to monotherapy. Another study showed that palbociclib sensitized both tumor cell lines and autochthonous mouse tumors to radiation in medulloblastoma.[5] Similar results are seen in hepatocellular carcinoma,[7] cholangiocarcinoma, and non-small cell lung cancer[11] cell lines. Jointly, these studies suggest that palbociclib may be a promising drug to increase the therapeutic ratio of RT.

Conclusions

The use of RT in patients with metastatic breast cancer receiving palbociclib resulted in minimal grade 1 to 2 and no grade 3+ toxicities. This preliminary work suggests that RT in this patient population is safe and feasible. Subsequent studies with longer follow-up are needed to confirm these results and investigate further use of palbociclib with RT.

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