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Review Article

CDK 4/6 inhibitors combined with radiotherapy: A review of literature

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ABSTRACT

Cyclin-dependent kinase 4 and 6 inhibitors (CDK4/6i) namely palbociclib, ribociclib and abemaciclib were granted approval by the European Medicines Agency (EMA) between 2017 and 2018. They are currently prescribed in combination with hormone therapy to treat hormone receptor positive, HER2 negative metastatic or locally advanced breast cancer. Their combination with radiotherapy raises safety concerns as preclinical data enlightened their possible synergistic effect. Moreover, data about toxicity when combining CDK4/6i with radiotherapy are scarce. This review of literature focused on the use of CDK4/6i combined with radiotherapy. It aimed at listing every published data about such combination so as to understand its possible resulting toxicity in metastatic breast cancer.

Contents

1. Introduction

Since 2017, cyclin 4 and 6 dependent kinase inhibitors (CDK4/6i) have been used to treat women with ER-positive, HER2-negative metastatic or locally advanced breast cancer. Their combination with hormone therapy such as aromatase inhibitors or fulvestrant produce a synergistic effect, which prevents cancer cell division [1–7]. Palbociclib was granted European approval based on the PALOMA 2 and 3 trials [8–10]. Ribociclib received European approval based on MONALEESA 2 and 3 trials [11–15]. Recently, an improvement in overall survival (OS) was reported in MONALEESA-7 [16]. Abemaciclib received European approval based on MONARCH 2 and 3 studies [17–19]. The latest update of MONARCH 2 showed a significant improvement of OS. Tolerance remained the same whatever the combined hormone therapy. CDK4/6 inhibitors (CDK4/6i) pharmacological characteristics are listed in Table 1.

Metastatic breast cancer patients often need palliative radiotherapy. A study about the benefit of curative-intent radiotherapy on primary tumor or oligometastases is currently ongoing and, its

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Table 1
Characteristics of approved CDK4/6 inhibitors [1–7].

CDK4/6 inhibitors	Palbociclib	Ribociclib	Abemaciclib
Approval	- Hormone receptor positive, HER2 negative metastatic or locally advanced breast cancer - in combination with aromatase inhibitors or fulvestrant (in pre- or post-menopausal patients combined with LH-RH agonist) - women treated with hormone therapy before	- Hormone receptor positive, HER2 negative metastatic or locally advanced breast cancer - in combination with aromatase inhibitors or fulvestrant (in pre- or post-menopausal patients combined with LH-RH agonist) - as first-line treatment or after hormone therapy	Hormone receptor positive, HER2 negative metastatic or locally advanced breast cancer In combination with aromatase inhibitors or fulvestrant (in pre- or post-menopausal patients combined with LH-RH agonist) - as first-line treatment or after hormone therapy
Most frequent side effects	**All grades:** Neutropenia, infections, leucopenia, fatigue, nausea, stomatitis, anaemia, alopecia et diarrhea. **Grade 3 and 4:** Neutropenia, leucopenia, anemia, fatigue, infections	**All grades:** Neutropenia, leucopenia, headaches, back pain, nausea, fatigue, diarrhea, vomiting, rash, constipation, alopecia. **Grade 3 and 4**: Neutropenia, nausea, leucopenia, abnormal liver functions, lymphopenia, hypo-phosphatemia, vomiting, fatigue, back pain	**All grades:** Diarrheas, infections, neutropenia, anemia, fatigue, nausea, vomiting, lack of appetite **Grade 3 and 4:** Neutropenia, diarrhea, leucopenia, anemia and infections
Dose schedule	1 cycle = Daily dose 125 mg (1 pill) for 21 days + 7 days without treatment	1 cycle = Daily dose 600 mg (3 pills) for 21 days + 7 days without treatment	150 mg twice a day, without interruption
Half-life	28.8 h	32 h	24.8 h
5 half-lives	6 days	6.7 days	5.2 days

preliminary results are promising [20–23]. Yet, little is known about the safety of the combination of CDK4/6i and radiotherapy. Preclinical studies suggested CDK4/i had a radiation-sensitizing effect on human cancer cell lines as they inhibited repair mechanisms of double DNA stand breaks [24–37]. Indeed, CDK4/6i may increase radiotherapy antitumor effect by first, controlling cell progression from G1 phase to the more radioresistant S phase and secondly, by inhibiting repair mechanisms of DNA double-strand break [24–37]. Moreover, when radiotherapy and CDK4/6i were combined, markers of DNA damage (γH2AX) and apoptosis (cPARP) increased. Conversely, acute gastrointestinal toxicity in mice was observed with concomitant palbociclib and fractionated abdominal radiotherapy [34]. Grade 3 enterocolitis was observed in one patient after palbociclib and palliative radiotherapy combination [35]. Thus, a careful analysis of every clinical data is required before greenlighting the radiotherapy-CDK4/6i combination. Such step will be all the more crucial as CDK4/6i could be used in other cancers [25]. Data about toxicity due to the combination of CDK4/6i with radiotherapy are rare. This review of literature aimed at listing reported toxicities caused by CDK4/6i combined with radiotherapy.

2. Materials and methods

A systematic assessment of literature articles was performed by searching in Pubmed Medline and Cochrane databases until January 1st 2020. The following keywords were used: "CDK4/6i"; "palbociclib"; "ribociclib"; "abemaciclib"; and "radiotherapy", "radiation", "radiation therapy". As to *in vivo* and *in vitro* studies, they were excluded. Nine hundred and eighteen articles were identified. After focusing on titles and abstracts, 19 articles remained. Then, after focusing on CDK4/6i, only 7 articles were included in the final analysis.

3. Results

The 7 publications described the outcome of 92 radiotherapy procedures combined with CDK4/6i in 59 patients. Thirty-five patients (59%) received palliative radiotherapy for bone, brain or liver metastases from breast cancer. Twenty-four patients (41%) had curative radiotherapy for oligometastatic disease. Some studies pooled patients who had received different CDK4/6i and different types of radiotherapy treatments. Other studies analysed the number of irradiated sites. Two studies pooled patients who had different treatment protocols including concurrent, pre or post CDK4/6i combined with radiotherapy. The characteristics of all 7 studies included are summarized in Table 2.

3.1. Palbociclib

The first study about the radiotherapy/palbociclib combination was published in January 2018 [38]. Five patients received palliative radiotherapy for breast cancer bone metastases. It was combined with ribociclib and letrozole as first-line treatment [43]. 3-D conformal radiotherapy was performed in 4 patients (20 Gy, 5 fractions on lumbar spine, hip and femur) whereas VMAT (Volumetric Modulated Arc Therapy) was chosen once (30 Gy, 5 fractions on the femur). Radiotherapy was concurrent to first cycle of ribociclib. Toxicities were assessed 3 weeks post-radiotherapy. Grade 3–4 neutropenia was reported after VMAT femoral neck. Grade 3–4 diarrhea/vomiting were reported after right hip radiation. Treatment fields and dosimetry were not reported.

Five patients with metastatic breast cancer had concurrent radiotherapy + palbociclib + fulvestrant. Four patients had palliative-intent radiotherapy on bone lesions (20 Gy/5fr). One patient had curative-intent radiotherapy on liver lesions (60 Gy/10fr). Information about follow-up was not available. Pain relief was achieved in 100% of the palliative patients. The patient who received curative doses was progression-free after treatment. No grade 3 radio-induced toxicity was reported in this small series. One grade 2 mucositis was reported but the correlation between such toxicity and any treatment -either systemic or radiotherapy- was not described. Patients experienced usual palbociclib-induced hematological toxicities such as grade 3 thrombopenia (n = 2), neutropenia (n = 2) and anemia (n = 1). Such data was contradicted in October 2018 by the publication of a case

Table 2
Summary of all restrospective studies and case reports.

First Author	Dates of publication	Molecule	Design	Number of patients	Combination	Radiotherapy	Radiation-induced toxicity grade ≥ 2 or treatment delay
PALBOCICLIB							
[38] **Hans S**	**01-2018**	Palbociclib plus Fulvestrant	Retrospective cohort	N = 5	Concurrent	- **Palliative** : 4 patients with bone metastases : 20 Gy/5fr (1 sacral iliac 1 scapula 2 vertebra) - **Curative :** 1 patient with liver metastases : 60 Gy/10fr	None
[35]**Kawamoto,**	**10-2018**	Palbociclib + Fulvestrant	Case report	N = 1	Concurrent	30 Gy /10fr, Left iliac bone and first sacral vertebrae.	Bloating, bloody diarrhoea and grade 3 colitisConfirmed by CT scan and colonoscopy, to the irradiation field.
[39] **Chowdhary,**	**1-2019**	Palbociclib + Fulvestrant (n = 6) or + letrozole (n = 10)	Retrospective cohort	N = 16	4 before RT (25.0%), −5 concurrently (31.3%), −7 after RT (43.8%).	−3 whole brain,30 Gy/10fr to 35 Gy/14fr −1 stereotactic radiosurgery frontal cavity 25 Gy/5fr. −1 mediastinum IMRT 36 Gy/18fr. −18 bone (11 axial skeleton, 4 pelvis, 3 extremity), − 1 Right calvarium IMRT 37.5 Gy/15fr − 1 cervical vertebrae SBRT 18 Gy/1fr	No acute/late toxicity at 14.7 months
[40] **Messer J.A.,**	**5-2019**	Palbociclib plus Fulvestrant	Case report	N = 1	concurrent	- supraclavicular lymph node, 60 Gy/30fr, 3DCRT	Esophagitis after 5 fr, dermatitis grade 2 after 20 fr dysphagia grade 3 requiring a break in treatment. 1 month hospitalization and finish the radiation without palbociclib 20 Gy/10fr.
[41] **Ippolito.**	**5-2019**	-n = 13 (19 tt) Palbociclib plus Letrozole or Fulvestrant -N = 3 (5 ttt) Ribociclib plus Letrozole	Retrospective cohort	N = 16	concurrent	−11 patients undergoing palliative bone radiotherapy (median dose 30 Gy, 8–36 Gy). −5 oligo metastatic patients (31.2%) treated with higher doses (median dose 50 Gy, range 39.6–60 Gy). −19 3D-CRT, 2 IMRT, 3 VMAT	2 early interruptions due to grade 2 skin toxicity (6.3%)
[42] **Figura**	**8-2019**	-Palbociclib (n = 10; 67%) or -Abemaciclib (n = 5; 33%).	Retrospective cohort	N = 15, 42 sites irradiations	- concurrently 18(43%) - before 9 (21%) - after 15 (36%)	-Median follow-up 9 month all : Stereotactic Body Radiotherapy IMRT 6Mv	2 radionecrosis (5%),
RIBOCICLIB							
[43] **Meattini**	**12-2018**	Ribociclib plus Letrozole	Retrospective cohort	N = 5	Concurrent	- bone metastases (femoral neck, hip, lumbar and cervical spine) −1 VMAT (30 Gy/5fr) −4 3D-CRT(20 Gy/5fr)	1 grade 2 diarrhea, right hip ribociclib suspension 2 weeks No toxicity at 3 months

(*continued on next page*)

Table 2 (*continued*)

First Author	Dates of publication	Molecule	Design	Number of patients	Combination	Radiotherapy	Radiation-induced toxicity grade ≥ 2 or treatment delay
[41] **Ippolito**	**5-2019**	-n = 13 (19 tt) Palbociclib plus Letrozole or Fulvestrant -n = 3 (5 tt) Ribociclib plus Letrozole	Retrospective cohort	N = 16	Concurrent	−11 patients undergoing palliative bone radiotherapy (median dose 30 Gy, 8–36 Gy. −5 oligo metastatic patients (31.2%) treated with higher doses (median dose = 50 Gy, range 39.6–60 Gy). −19 3D-CRT 2 IMRT 3 VMAT	2 early interruptions (one grade 2 dermatitis (6.3%))
ABEMACICLIB							
[42] **Figura**	**8-2019**	-Palbociclib (n = 10; 67%) or -Abemaciclib (n = 5; 33%). −16 Aromasine inhibitors, 20 Fulvestrant	Retrospective cohort	N = 15 (42 treatments)	-Concurrent 18 (43%) -pre: 9 (21%) -post: 15 (36%)	-Median follow-up 9 month Technique: Stereotactic Body Radiotherapy (IMRT 6Mv)	2 radionecrosis (5%),

Abbreviations: fr: fraction; tt: treatment.

report [35] about a patient with no medical history of digestive tract disease. He received palbociclib + fulvestrant concurrently with 3D conformational radiotherapy (30 Gy/10fr) on the left iliac bone and first sacral vertebrae. Three days after radiotherapy completion, the patient experienced grade 3 colitis. CT scan and colonoscopy revealed bowel wall thickening corresponding to inflammatory disorders. The patient had no radio-sensitizing comorbidity such as an inflammatory intestinal disease and no radio-sensitizing treatment. The doses on the colon were limited (Dmax = 31.9 Gy so 106.3% of the prescribed dose, V_{10Gy} = 21 cc, V_{20Gy} = 18 cc). Palbociclib was therefore suspected of causing this unusual toxicity in radiation fields. In January 2019, a retrospective study reported outcome of 16 breast cancer patients with bone metastases radiotherapy and palbociclib [39]. Six patients had concurrent fulvestrant and ten had letrozole. Palbociclib was administered at different times from radiotherapy. Eleven patients had sequential treatment combination (palbociclib was prescribed before radiotherapy in 4 patients (25%) and after in 7 patients (43.8%)) whereas 5 patients had a concurrent administration (31.2%). The irradiated sites were bone (11 axial skeleton among which 2 stereotactic radiosurgery, 4 pelvic, 3 extremities), brain (3 whole brain radiotherapy, 1 stereotactic radiosurgery) and mediastinum (1). Bone stereotactic radiosurgery delivered 18 Gy/1fraction on C2 vertebrae and 30 Gy/3 fractions on the left iliac bone. A dose of 25 Gy/5 fractions brain stereotactic radiosurgery was delivered post-surgery. Other treatments were mostly 3D conformational (2 IMRT in 16 patients) which delivered 30–37 Gy in 10–15 fractions. Median follow-up was 14.7 months. Pain relief and local control were achieved in all patients. Before radiotherapy, 4 patients developed leucopenia (25%), 5 had neutropenia (31.3%) and 1 developed thrombopenia (6,3%). After radiotherapy, 5 patients developed leucopenia (31.3%), 1 patient showed neutropenia (6.3%) and 3 patients developed thrombopenia (18.8%). Usual palbociclib induced hematological toxicities were grades 1 to 2. No grade ≥ 2 acute or late radio-induced dermatological, neurological or gastrointestinal toxicity was observed. No significant increase in acute or late toxicities with CDK4/6i and radiotherapy combination was reported but when palbociclib was administered alone. In addition, toxicity remained the same regardless of the irradiated site, the type of hormone therapy and the chronology of palbociclib and radiotherapy initiation. Authors concluded that, as toxicity was low, the radiotherapy/palbociclib combination could be used safely. The results of a 2019 case report about 60 Gy, 30 fractions curative-intent radiotherapy were less reassuring [40]. The patient with metastatic breast cancer received radiation treatment to a metastatic supraclavicular and axillary lymph node flow. 3-D conformal radiotherapy was performed on one treatment field. It was combined with concurrent palbociclib-fulvestrant. No customized bolus was used during radiotherapy. The maximum dose was 63.6 Gy, the equivalent of 106% of the prescribed dose. After 5 fractions, the patient developed odynophagia although the planned doses to esophagus were limited ($D_{max\ esophagus}$ = 27 Gy, D_{mean} = 9 Gy). After 40 Gy (20 fractions), she developed grade 2 skin toxicity. *In vivo* dosimetry showed no significant difference from planned dosimetry. The following day, the patient developed grade 3 dysphagia and dermatitis as well as grade 2 pain requiring IV hydration in hospital. Palbociclib and radiotherapy were stopped for 1 month. The remaining 20 Gy were delivered without restarting palbociclib and it was well-tolerated. No information was available regarding the management of hormone therapy. Palbociclib was restarted 1 month after radiotherapy completion. Six months later, images showed no sign of disease and side effects had totally healed. In May 2019, Ippollito et al. published a retrospective evaluation of the early toxicity of concurrent radiotherapy combined with palbociclib or ribociclib in metastatic breast cancer patients [41]. Thirteen out of the 16 patients (81.3%) received palbociclib combined with letrozole or fulvestrant. Most patients (68.7%) received palliative radiotherapy to bones. The median dose was 30 Gy (range: 8–36 Gy). Five patients (31.2%) received higher doses (median dose 50 Gy, range: 39.6–60 Gy) on oligo-metastatic or oligo-progressive cancer sites. The most common toxicity was hematologic. Neutropenia was common (grade 2 = 12.5%, grade 3 = 25%, grade 4 = 6.3%). Sixty per cent of the patients with grade ≥ 3 neutropenia had already experienced neutropenia during previous cycles of palbociclib. Because of hematologic side effects, 1 patient suspended palbociclib 7 days earlier. Among the 13 patients on palbociclib, 2 (15.3%) suspended radiotherapy because of acute

Table 3
Characteristics of the publications (59 patients, 92 radiotherapy treatments).

CDK4/6 inhibitors	Number of patients included	Palbociclib [38–42]	Ribociclib [41,43]	Abemaciclib [42]
Number of patients	59 (100%)	46 (79%)	8 (13.5%)	5 (8.47%)
Irradiation intent	Palliative (n = 32) Curative (n = 27)	Palliative (n ≥ 16)* Curative (n ≥ 19)*	Palliative (n ≥ 5)* Curative (n ≥ 0)*	Curative (n = 5)
Irradiated sites (n = 92)		spine, pelvis bone extremity, brain, mediastinum, supraclavicular lymphadenopathy, calvarium bone	bone	brain
Combined hormone therapy		Fulvestrant (n = 13) Letrozole (n = 10)	Letrozole	Not reported
Type of radiotherapy treatment		3DCRT/IMRT/VMAT/SBRT	VMAT /3DCRT	SBRT
Sequence of administration : CDK4/6-RT	Pre : 13 Concurrent : 51 Post : 22	≥ 4 pre** ≥25 concurrent** ≥7 post**	Concurrent	Not reported
Hematological toxicities grade ≥ 3 (11 = 18.6%)		5 Myelotoxicity reported after systemic treatment	1 Myelotoxicity reported after systemic treatment 1 grade greater than 3	No increase of hematotoxicity
Toxicity in the irradiation field grade ≥ 3 (6.7%)		−1 colitis −1 œsophagitis + skin		2 radionecrosis but no information about CDK4/6(palbociclib or abemaciclib)

* Patients from Ippolito trial are included here but their precise number is not reported.
** Patients from the Figura trial are included but their precise number is not reported.

Table 4
Currently recruiting clinical trials testing radiotherapy combined with CDK4/6 inhibitors.

Trial number	Primary tumour	Molecules	Radiotherapy	AssociationRT/ CDK4/6inhibitors	Primary objective	Type of study	Inclusion goal
PALBOCICLIB							
NCT03691493 (ASPIRE)	Breast Cancer Patients With Bone Metastasis	Concurrent Palbociclib and Hormone Therapy	Conventionally fractionated radiotherapy on bone metastases (on 5–10 days)	Concurrent	3-month response rate	Phase 2 Interventional single arm	42
NCT03870919 (PALATINE)	Breast Cancer Treatment Naive, Stage IV ER+, HER2-	Palbociclib + letrozole	Local breast treatment, (surgery (conservative or mastectomy) with or without radiotherapy, or exclusive radiotherapy	Concurrent	2-year overall survival	Not Applicable	200
NCT03024489	Head and Neck Cancer Locally Advanced	Palociclib + Cetuximab	IMRT 70 Gy/35fr on primary tumor	Concurrent	Dose-limiting toxicities and recommended dose	Phase I/II	33
RIBOCICLIB							
NCT03355794	Children Gliomas	Ribociclib and Everolimus	Standard radiation therapy	Sequential : Ribociclib strated 2–4 weeks after RT completion	Adverse events 6 months Individual toxicities and incidence of significant delays maximum tolerated dose and/or recommended phase 2 dose	Phase I Interventional	24
ENDOCRINE THERAPY (including CDK4/6 inhibitors or mTOR inhibitors)							
NCT03750396 (CLEAR)	ER-positive/HER2-negative Oligo-metastatic Breast Cancer	CDK4/6 inhibitors or mTOR inhibitors	Stereotactic body radiotherapy	NA	Progression-free survival	Phase II Interventional	110

side effects. One patient with skin metastases suspended chest wall radiotherapy 1 week (at 48 Gy out of 50 Gy prescribed) due to grade 2 skin toxicity. Another one suspended radiotherapy for 2 days but authors provided no information about irradiated site and type of toxicity in the article. Besides, radiotherapy characteristics in these 2 patients were not available. Median follow-up was 6.3 months. All patients experienced pain relief. Authors' conclusion was that high-grade hematological toxicities were the same as those expected with these systemic treatments and had no impact on the radiotherapy treatment for most patients. In August 2019, Figura et al. published a retrospective analysis of 15 patients who received stereotactic radiotherapy for 42 brain metastases. Radiotherapy was performed within the 6 months pre- or post-CDK4/6i treatment (n = 10 palbociclib (67%), n = 5 abemaciclib (33%)) [42]. Dose and fractionation were heterogeneous (from 24 Gy in 1 fraction to 20 Gy in 5 fractions). Two radiation courses out of 42 (5%) led to clinical radionecrosis after 4 fractions. It was managed with steroids and bevacizumab. Radiotherapy dose,

CDK4/6i and combined hormonal therapy were not reported. Local control after one year was 88%. Stereotactic radiation to brain metastasis was well tolerated during CDK 4/6i administration.

Twenty-eight patients received concurrent palbociclib and radiotherapy combination only. Two clinical cases presented with grade 3 colitis, grade 2 dermatitis and grade 3 dysphagia [35,40]. The remaining 26 patients from the retrospective studies experienced grade 2 skin toxicity which led to 2 early treatment interruptions [38,39,41]. Such data is summarized in Table 2.

3.2. Ribociclib

A retrospective study was published in 2018. Five patients received palliative radiotherapy on breast cancer bone metastases. It was combined with ribociclib and letrozole as first-line treatment [43]. 3-D conformal radiotherapy was performed in 4 patients (20 Gy, 5 fractions on lumbar spine, hip and femur) whereas VMAT was chosen once (30 Gy, 5 fractions on the femur). Radiotherapy was concurrent to first cycle of ribociclib. Toxicities were assessed 3 weeks post-radiotherapy. Grade 3–4 neutropenia was reported after VMAT femoral neck. Grade 3–4 diarrhea/vomiting were reported after right hip radiation. Treatment fields and dosimetry were not reported. However, given the treated locations, such side effects probably resulted more from systemic treatment than radiotherapy. Ribociclib had to be suspended for 2 weeks in both patients. Letrozole was continued. Pain was relieved in 100% of the cases. At 3-month assessment, 3 patients were stable, 2 had partial response. No other abnormal toxicity was reported.

In Ippolito et al. study, 3 patients out of 16 were prescribed ribociclib in combination with letrozole. One patient on ribociclib concurrent to radiotherapy experienced grade 2 neutropenia. No other radio-induced toxicity was reported but the irradiated sites, the radiotherapy technique and doses combined with ribociclib were specified in the article. Every data is summarized in Table 2.

3.3. Abemaciclib

In the retrospective analysis by Figura et al. about brain metastases radiotherapy with curative intent, 5 out of the 15 patients received abemaciclib [42]. No information about CDK4/6i subgroups was given thus it is impossible to know if the patients experiencing radionecrosis after 4 fractions were on abemaciclib or palbociclib. Such data is summarized in Table 2.

4. Discussion

With emergence of CDK4/6i along with their expanding indications, it seems essential to understand the role played by and the risks of the combination of radiotherapy with CDK4/6i. We aimed at bringing together every published data about this issue and, to our knowledge; this article is the first attempt to try to do so.

In many cancer subtypes, preclinical studies [24–37] suggested that CDK4/6i have a radiation-sensitizing effect on tumor cells. In daily practice, CDK4/6i have been prescribed for more than 2 years in metastatic breast cancer. The issue of their safe combined use with palliative or curative radiotherapy has only been evaluated through limited retrospective data. Like in pre-clinical studies, the most tested molecule was palbociclib as it was the first to be granted approval. This review of literature included 59 patients among whom 46 had radiotherapy + palbociclib (79%), 8 had radiotherapy + ribociclib (13.5%) and 5 had abemaciclib + radiotherapy (8.47%) (Table 3). Whatever the goal of these therapeutic combinations– to relieve pain, to control irradiated lesions- it was always achieved when reported. Radiotherapy technique and doses were common practices. In more than 50% of the cases, CDK4/6i were administered concurrently. Regarding toxicities, 4 out of the 59 patients (6.77%) had $\geq$ grade 3 acute toxicities due to radiotherapy, 2 (3.38%) had $\geq$ grade 2 severe toxicities which required temporary radiotherapy suspension. Severe toxicities were therefore reported in more than 10% of the patients, which seemed inacceptable in first-line metastatic treatment. Hematological toxicity was related to CDK4/6i when combined with radiotherapy in 18.6% of the cases analysed in our review. The number of hematological toxicities did not seem to inflate with radiotherapy.

In addition, only one study evaluated late toxicities (over 3 months) caused by ribociclib + radiotherapy [43]. Indeed, late toxicity due to concurrent CDK 4/6i requires further investigations. Indeed, without confirmed safety proof, it seems wiser to suspend CDK4/6i 5 half-lives before and after radiotherapy. This can easily be achieved as CDK4/6 molecules have a short half-life that requires between 5 and 7 days arrest (Table 1). Meanwhile, hormone-therapy can be pursued during radiation course.

Currently prospective clinical data about CDK4/6i and radiotherapy are scarce. Additional safety data should be reported in open and ongoing clinical trials testing CDK4/6i-radiotherapy combination The ongoing prospective phase 2 ASPIRE trial is assessing radiotherapy combined with palbociclib and hormone therapy for bone metastases in breast cancer patients whereas PALATINE prospective trial will assess local breast treatment, (surgery and/or radiotherapy) in advanced breast cancer (Table 4).

5. Conclusion

Most pre-clinical data showed CDK4/6i have a synergistic radiosensitizing effect. Such data seems to be in accordance with retrospective clinical studies, which show that more than 10% of severe toxicities occur in radiation fields. Precautionary principle requires CDK4/6i are suspended five half-lives before and after radiotherapy. The results of ongoing prospective clinical trials assessing the combination of CDK4/6i and radiotherapy are expected to bring additional answers about its safe use.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

References

[1] IBRANCE (palbociclib), inhibiteur de protéine kinase. Haute Aut Santé n.d. https://www.has-sante.fr/jcms/c_2964747/fr/ibrance-palbociclib-inhibiteur-de-proteine-kinase (accessed September 19, 2019).
[2] KISQALI. Haute Aut Santé n.d. https://www.has-sante.fr/jcms/c_2827573/fr/kisqali (accessed September 19, 2019).
[3] VERZENIOS. Haute Aut Santé n.d. https://www.has-sante.fr/jcms/c_2892921/fr/verzenios (accessed September 19, 2019).
[4] Lapenna S, Giordano A. Cell cycle kinases as therapeutic targets for cancer. Nat Rev Drug Discov 2009;8:547–66. https://doi.org/10.1038/nrd2907.
[5] Beaver JA, Amiri-Kordestani L, Charlab R, Chen W, Palmby T, Tilley A, et al. FDA approval: palbociclib for the treatment of postmenopausal patients with estrogen receptor-positive, HER2-negative metastatic breast cancer. Clin Cancer Res Off J Am Assoc Cancer Res 2015;21:4760–6. https://doi.org/10.1158/1078-0432.CCR-15-1185.
[6] Shah A, Bloomquist E, Tang S, Fu W, Bi Y, Liu Q, et al. FDA Approval: ribociclib for the treatment of postmenopausal women with hormone receptor-positive, HER2-negative advanced or metastatic breast cancer. Clin Cancer Res Off J Am Assoc Cancer Res 2018;24:2999–3004. https://doi.org/10.1158/1078-0432.CCR-17-2369.
[7] FDA OKs Abemaciclib for ER+, HER2- Breast Cancer. Cancer Discov 2017;7:OF1. https://doi.org/10.1158/2159-8290.CD-NB2017-141.
[8] Cristofanilli M, Turner NC, Bondarenko I, Ro J, Im S-A, Masuda N, et al. Fulvestrant plus palbociclib versus fulvestrant plus placebo for treatment of hormone-receptor-positive, HER2-negative metastatic breast cancer that progressed on previous endocrine therapy (PALOMA-3): final analysis of the multicentre, double-blind, phase 3 randomised controlled trial. Lancet Oncol 2016;17:425–39. https://doi.org/10.1016/S1470-2045(15)00613-0.

[9] Finn RS, Crown JP, Lang I, Boer K, Bondarenko IM, Kulyk SO, et al. The cyclin-dependent kinase 4/6 inhibitor palbociclib in combination with letrozole versus letrozole alone as first-line treatment of oestrogen receptor-positive, HER2-negative, advanced breast cancer (PALOMA-1/TRIO-18): a randomised phase 2 study. Lancet Oncol 2015;16:25–35. https://doi.org/10.1016/S1470-2045(14)71159-3.
[10] Turner NC, Slamon DJ, Ro J, Bondarenko I, Im S-A, Masuda N, et al. Overall survival with palbociclib and fulvestrant in advanced breast cancer. N Engl J Med 2018;379:1926–36. https://doi.org/10.1056/NEJMoa1810527.
[11] Janni W, Alba E, Bachelot T, Diab S, Gil-Gil M, Beck TJ, et al. First-line ribociclib plus letrozole in postmenopausal women with HR+, HER2− advanced breast cancer: tumor response and pain reduction in the phase 3 MONALEESA-2 trial. Breast Cancer Res Treat 2018;169:469–79. https://doi.org/10.1007/s10549-017-4658-x.
[12] Yardley DA. MONALEESA clinical program: a review of ribociclib use in different clinical settings. Future Oncol 2019;15:2673–86. https://doi.org/10.2217/fon-2019-0130.
[13] Hortobagyi GN, Stemmer SM, Burris HA, Yap YS, Sonke GS, Paluch-Shimon S, et al. Updated results from MONALEESA-2, a phase III trial of first-line ribociclib plus letrozole versus placebo plus letrozole in hormone receptor-positive, HER2-negative advanced breast cancer. Ann Oncol Off J Eur Soc Med Oncol 2019. https://doi.org/10.1093/annonc/mdz215.
[14] Slamon DJ, Neven P, Chia S, Fasching PA, De Laurentiis M, Im S-A, et al. Phase III randomized study of ribociclib and fulvestrant in hormone receptor-positive, human epidermal growth factor receptor 2–negative advanced breast cancer: MONALEESA-3. J Clin Oncol 2018;36:2465–72. https://doi.org/10.1200/JCO.2018.78.9909.
[15] Hortobagyi GN, Stemmer SM, Burris HA, Yap Y-S, Sonke GS, Paluch-Shimon S, et al. Ribociclib as first-line therapy for HR-positive, advanced breast cancer. N Engl J Med 2016;375:1738–48. https://doi.org/10.1056/NEJMoa1609709.
[16] Im S-A, Lu Y-S, Bardia A, Harbeck N, Colleoni M, Franke F, et al. Overall survival with ribociclib plus endocrine therapy in breast cancer. N Engl J Med 2019;381:307–16. https://doi.org/10.1056/NEJMoa1903765.
[17] Johnston S, Martin M, Leo AD, Im S-A, Awada A, Forrester T, et al. MONARCH 3 final PFS: a randomized study of abemaciclib as initial therapy for advanced breast cancer. Npj Breast Cancer 2019;5:1–8. https://doi.org/10.1038/s41523-018-0097-z.
[18] Goetz MP, Toi M, Campone M, Sohn J, Paluch-Shimon S, Huober J, et al. MONARCH 3: abemaciclib as initial therapy for advanced breast cancer. J Clin Oncol Off J Am Soc Clin Oncol 2017;35:3638–46. https://doi.org/10.1200/JCO.2017.75.6155.
[19] Sledge GW, Toi M, Neven P, Sohn J, Inoue K, Pivot X, et al. MONARCH 2: abemaciclib in combination with fulvestrant in women with HR+/HER2- advanced breast cancer who had progressed while receiving endocrine therapy. J Clin Oncol Off J Am Soc Clin Oncol 2017;35:2875–84. https://doi.org/10.1200/JCO.2017.73.7585.
[20] Olson R, Senan S, Harrow S, Gaede S, Louie A, Haasbeek C, et al. Quality of life outcomes after stereotactic ablative radiation therapy (SABR) versus standard of care treatments in the oligometastatic setting: a secondary analysis of the SABR-COMET randomized trial. Int J Radiat Oncol Biol Phys 2019;105:943–7. https://doi.org/10.1016/j.ijrobp.2019.08.041.
[21] Mauro GP, de Andrade CH, Stuart SR, Mano MS, Marta GN. Effects of locoregional radiotherapy in patients with metastatic breast cancer. Breast Edinb Scotl 2016;28:73–8. https://doi.org/10.1016/j.breast.2016.05.001.
[22] Nguyen DHA, Truong PT, Alexander C, Walter CV, Hayashi E, Christie J, et al. Can locoregional treatment of the primary tumor improve outcomes for women with stage IV breast cancer at diagnosis?. Int J Radiat Oncol Biol Phys 2012;84:39–45. https://doi.org/10.1016/j.ijrobp.2011.11.046.
[23] Khodari W, Sedrati A, Naisse I, Bosc R, Belkacemi Y. AROME (Association of Radiotherapy and Oncology of the Mediterranean arEa; www.aromecancer.org). Impact of loco-regional treatment on metastatic breast cancer outcome: a review. Crit Rev Oncol Hematol 2013;87:69–79. https://doi.org/10.1016/j.critrevonc.2012.12.005.
[24] Hagen KR, Zeng X, Lee M-Y, Tucker Kahn S, Harrison Pitner M, Zaky SS, et al. Silencing CDK4 radiosensitizes breast cancer cells by promoting apoptosis. Cell Div 2013;8:10. https://doi.org/10.1186/1747-1028-8-10.
[25] Whittaker S, Madani D, Joshi S, Chung SA, Johns T, Day B, et al. Combination of palbociclib and radiotherapy for glioblastoma. Cell Death Discov 2017;3:17033. https://doi.org/10.1038/cddiscovery.2017.33.
[26] Whiteway SL, Harris PS, Venkataraman S, Alimova I, Birks DK, Donson AM, et al. Inhibition of cyclin-dependent kinase 6 suppresses cell proliferation and enhances radiation sensitivity in medulloblastoma cells. J Neurooncol 2013;111:113–21. https://doi.org/10.1007/s11060-012-1000-7.
[27] Hashizume R, Zhang A, Mueller S, Prados MD, Lulla RR, Goldman S, et al. Inhibition of DNA damage repair by the CDK4/6 inhibitor palbociclib delays irradiated intracranial atypical teratoid rhabdoid tumor and glioblastoma xenograft regrowth. Neuro-Oncol 2016;18:1519–28. https://doi.org/10.1093/neuonc/now106.
[28] Huang C-Y, Hsieh F-S, Wang C-Y, Chen L-J, Chang S-S, Tsai M-H, et al. Palbociclib enhances radiosensitivity of hepatocellular carcinoma and cholangiocarcinoma via inhibiting ataxia telangiectasia–mutated kinase–mediated DNA damage response. Eur J Cancer 2018;102:10–22. https://doi.org/10.1016/j.ejca.2018.07.010.
[29] Hickson I, Zhao Y, Richardson CJ, Green SJ, Martin NMB, Orr AI, et al. Identification and characterization of a novel and specific inhibitor of the ataxia-telangiectasia mutated kinase ATM. Cancer Res 2004;64:9152–9. https://doi.org/10.1158/0008-5472.CAN-04-2727.
[30] COPERNIC project investigators, Granzotto A, Benadjaoud MA, Vogin G, Devic C, Ferlazzo ML, et al. Influence of nucleoshuttling of the ATM protein in the healthy tissues response to radiation therapy: toward a molecular classification of human radiosensitivity. Int J Radiat Oncol Biol Phys 2016;94:450–60. https://doi.org/10.1016/j.ijrobp.2015.11.013.
[31] Tao Z, Le Blanc JM, Wang C, Zhan T, Zhuang H, Wang P, et al. Coadministration of trametinib and palbociclib radiosensitizes KRAS-mutant non-small cell lung cancers in vitro and in vivo. Clin Cancer Res 2016;22:122–33. https://doi.org/10.1158/1078-0432.CCR-15-0589.
[32] Göttgens E-L, Bussink J, Leszczynska KB, Peters H, Span PN, Hammond EM. Inhibition of CDK4/CDK6 enhances radiosensitivity of HPV negative head and neck squamous cell carcinomas. Int J Radiat Oncol 2019;105:548–58. https://doi.org/10.1016/j.ijrobp.2019.06.2531.
[33] Wei L, Leibowitz BJ, Wang X, Epperly M, Greenberger J, Zhang L, et al. Inhibition of CDK4/6 protects against radiation-induced intestinal injury in mice. J Clin Invest 2016;126:4076–87. https://doi.org/10.1172/JCI88410.
[34] Lee C-L, Oh P, Xu ES, Ma Y, Kim Y, Daniel AR, et al. Blocking cyclin-dependent kinase 4/6 during single dose versus fractionated radiation therapy leads to opposite effects on acute gastrointestinal toxicity in mice. Int J Radiat Oncol 2018;102:1569–76. https://doi.org/10.1016/j.ijrobp.2018.07.192.
[35] Kawamoto T, Shikama N, Sasai K. Severe acute radiation-induced enterocolitis after combined palbociclib and palliative radiotherapy treatment. Radiother Oncol 2019;131:240–1. https://doi.org/10.1016/j.radonc.2018.09.020.
[36] Naz S, Sowers A, Choudhuri R, Wissler M, Gamson J, Mathias A, et al. Abemaciclib, a selective CDK4/6 inhibitor, enhances the radiosensitivity of non-small cell lung cancer *in vitro* and *in vivo*. Clin Cancer Res 2018;24:3994–4005. https://doi.org/10.1158/1078-0432.CCR-17-3575.
[37] Tai T-S, Lin P-M, Wu C-F, Hung S-K, Huang C-I, Wang C-C, et al. CDK4/6 inhibitor LEE011 is a potential radiation-sensitizer in head and neck squamous cell carcinoma: an in vitro study. Anticancer Res 2019;39:713–20. https://doi.org/10.21873/anticanres.13167.
[38] Hans S, Cottu P, Kirova YM. Preliminary results of the association of palbociclib and radiotherapy in metastatic breast cancer patients. Radiother Oncol 2018;126:181. https://doi.org/10.1016/j.radonc.2017.09.010.
[39] Chowdhary M, Sen N, Chowdhary A, Usha L, Cobleigh MA, Wang D, et al. Safety and efficacy of palbociclib and radiation therapy in patients with metastatic breast cancer: initial results of a novel combination. Adv Radiat Oncol 2019;4:453–7. https://doi.org/10.1016/j.adro.2019.03.011.
[40] Messer JA, Ekinci E, Patel TA, Teh BS. Enhanced dermatologic toxicity following concurrent treatment with palbociclib and radiation therapy: a case report. Rep Pract Oncol Radiother J Gt Cancer Cent Poznan Pol Soc Radiat Oncol 2019;24:276–80. https://doi.org/10.1016/j.rpor.2019.03.001.
[41] Ippolito E, Greco C, Silipigni S, Dell'Aquila E, Petrianni GM, Tonini G, et al. Concurrent radiotherapy with palbociclib or ribociclib for metastatic breast cancer patients: preliminary assessment of toxicity. Breast Edinb Scotl 2019;46:70–4. https://doi.org/10.1016/j.breast.2019.05.001.
[42] Figura NB, Potluri TK, Mohammadi H, Oliver DE, Arrington JA, Robinson TJ, et al. CDK 4/6 inhibitors and stereotactic radiation in the management of hormone receptor positive breast cancer brain metastases. J Neurooncol 2019. https://doi.org/10.1007/s11060-019-03260-6.
[43] Meattini I, Desideri I, Scotti V, Simontacchi G, Livi L. Ribociclib plus letrozole and concomitant palliative radiotherapy for metastatic breast cancer. The Breast 2018;42:1–2. https://doi.org/10.1016/j.breast.2018.08.096.