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Efficacy of cyclin-dependent kinase 4/6 inhibitors in combination with hormonal therapy in patients with recurrent granulosa cell tumor of the ovary: A case series

Benjamin B. Albright [a,b,*], Stephanie Shuey [b], Angeles Alvarez Secord [a], Laura J. Havrilesky [a], Andrew Berchuck [a], Rebecca A. Previs [a,c]

[a] Division of Gynecologic Oncology, Department of Obstetrics and Gynecology, Duke University Medical Center, Durham, NC 27710, USA
[b] Division of Gynecologic Oncology, Department of Obstetrics and Gynecology, University of North Carolina at Chapel Hill, Chapel Hill, NC 27599, USA
[c] Labcorp Oncology, Durham, NC 27560, USA

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ABSTRACT

Cyclin-dependent kinase inhibitors are approved in combination with hormonal therapy for treatment of hormone receptor expressing breast cancers. Activity in hormone receptor expressing gynecologic cancers has been postulated. Granulosa cell tumor of the ovary is one such cancer, which is relatively resistant to traditional cytotoxic chemotherapy. We report a case series of 7 heavily pre-treated patients with recurrent granulosa cell tumor of the ovary with a cyclin-dependent kinase inhibitor in combination with hormonal therapy, with 3 patients demonstrating partial response and 2 with stable disease. As of the data cutoff, 3 patients remained on treatment and 5 were alive, with true medians for duration of treatment and overall survival not reached (medians at data cutoff of 64 weeks and 62 months respectively). The treatment was generally well tolerated, with 1 patient choosing to discontinue treatment due to grade 3 fatigue. This regimen represents a possible option in the treatment of granulosa cell tumor of the ovary, warranting further prospective study for this unmet need in this indolent disease which often requires many lines of treatment.

1. Introduction

Adult granulosa cell tumors of the ovary are the most common type of malignant ovarian sex cord-stromal tumor (Young, 2005). Most patients present with a pelvic mass and undergo surgery. Depending on stage and risk factors, adjuvant systemic therapy may be recommended (Lee et al., 2008; Schumer and Cannistra, 2003; Chan et al., 2005; Cronjé et al., 1999; Malmström et al., 1994).

For those who develop recurrence, prospective data guiding management is limited although surgical resection remains a cornerstone of management (Sehouli et al., 2004; Mangili et al., 2013; Karalok et al., 2016). For patients with unresectable disease, systemic therapy with chemotherapy, hormones, anti-angiogenic agents, and/or radiation are options (Levin et al., 2018; Brown et al., 2014; Gurumurthy et al., 2014). In the recurrent setting, various endocrine therapy options including aromatase inhibitors, tamoxifen, megestrol acetate and leuprolide acetate may provide clinical benefit to patients whose tumor express steroid hormone receptors (HR) (van Meurs et al., 2014; Martikainen et al., 1989; Fishman et al., 1996; Emons and Schally, 1994; Briasoulis et al., 1997; Armstrong et al., 2022). Eventually, patients with recurrent disease may require multiple surgeries and additional lines of therapy due to resistance. Therefore, an unmet need for novel therapeutic options exists for this indolent cancer.

Palbociclib, abemaciclib, and ribociclib are reversible small molecule cyclin-dependent kinase (CDK) inhibitors selective for CDK4 and CDK6. When activated by cyclin D1, CDKs promote progression of cells from the G1 to the S phase. Estrogen stimulates CDK activity and proliferation by inducing expression of cyclin D1. Through CDK inhibition, these drugs induce G1 cell cycle arrest, thereby decreasing proliferation of sensitive tumor cells. Antiestrogen therapies act synergistically with CDK4/6 inhibitors to prevent signaling through the cyclin D–CDK4/6-retinoblastoma pathway, resulting in more potent inhibition of tumor growth compared to either agent alone (Scott et al., 2017).

Palbociclib was Food and Drug Administration (FDA)-approved for advanced HR-positive breast cancer in combination with an aromatase inhibitor or fulvestrant in 2015 (Pernas et al., 2018; IBRANCE, 2022).

* Corresponding author at: 170 Manning Dr, CB #7572, Chapel Hill, NC 27599, USA.
E-mail address: Benjamin_albright@med.unc.edu (B.B. Albright).

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Several follow-up trials demonstrated improved survival and manageable side effect profile (Finn et al., 2015; Turner et al., 2015; Cristofanilli et al., 2016; Finn et al., 2016; Turner et al., 2018). In breast cancer, HR-positivity is the only clinical predictor that consistently correlates with response to CDK inhibitors (Giannone et al., 2019). Given the interplay between these signaling pathways, evaluation of CDK4/6 inhibitors in combination with anti-estrogen therapies is ongoing in other HR-positive cancers, including gynecologic cancers.

Due to the relative rarity of granulosa cell tumors of the ovary, it is challenging to recruit patients to large prospective clinical trials. We report a single institution case series of seven patients with recurrent granulosa cell tumor who received a CDK4/6 inhibitor in combination with antiestrogen therapy.

2. Methods

This study included patients with recurrent adult granulosa cell tumor of the ovary treated with a CDK4/6 inhibitor in combination with hormonal therapy at a single academic institution who initiated treatment prior to June 30th, 2022. Cutoff for data collection was June 30th, 2023. Patients were retrospectively identified through a review of clinical and pharmacy records. Electronic medical records were reviewed, and relevant data abstracted, including initial cancer diagnosis, prior treatment history, course on the treatment of interest (including inhibin levels, treatment-related toxicities, and interval disease assessments with imaging), survival, and course after discontinuation of the treatment of interest.

As part of standard practice at our institution, patients were counseled by a health care provider about side effects, risks, benefits and the off-label use of CDK4/6 inhibitor therapy. Prior to each cycle of treatment, patients were evaluated by treating physician in a thorough assessment for treatment related toxicities, with a full history, physical examination, and laboratory panel including complete blood count with differential and comprehensive metabolic panel. Tumor response was assessed biochemically with inhibin A and B levels, and via computed tomography at intervals determined by the treating physician. Partial response was defined as documented shrinkage of some or all areas of disease on radiologic imaging without disease growth or new metastatic lesions, or increase in inhibin levels. Treatment was continued until unacceptable disease progression or toxicity. All treatment holds, dose reductions, and discontinuations were determined between the patient and treating physician based on treatment related toxicity and disease response.

This study was approved by the Duke University Institutional Review Board (Pro00110085) prior to initiation of data collection. Figures were created with STATA v17.0 (StataCorp, College Station, TX, USA).

3. Results

A total of 7 patients were identified with recurrent granulosa cell tumor of the ovary, treated with CDK4/6 inhibitor therapy in combination with hormonal therapy, initiated between February 2020 and March 2022. Patient and tumor characteristics are presented in Table 1. At the start of treatment, patient ages ranged from 42 to 73 years. Most patients had long disease courses, with a median of 13 years since diagnosis (range 5–36 years), and extensive prior treatment, including medians of 3 prior surgeries (range 1–13), and 6 prior lines of systemic therapy (range 1–14). Prior systemic treatments included various cytotoxic and hormonal therapies, including prior single agent letrozole in five patients for a median duration of 17 months (see Table S1). Three patients previously underwent radiation. All patients had elevations in inhibin A, inhibin B, or both at the time of treatment initiation.

Disease distribution at the time of treatment initiation varied, with 5 patients having abdominal/pelvic masses or carcinomatosis, 2 with liver metastases, 3 with nodal disease, and 1 with chest/lung disease. All three patients with next-generation sequencing results had alterations in *FOXL2* C134W and *TERT* promoter 124C > T, and all four tumors evaluated for microsatellite instability were microsatellite stable (see Table S2). Estrogen receptor and progesterone receptor expression status was only available for one patient (patient 3; ER-, PR+), who had a partial response despite lacking estrogen receptor expression.

All patients received palbociclib as the initial orally administered CDK4/6 inhibitor, dosed initially at 125 mg for days 1–21 for each 28-day cycle. Letrozole was utilized as hormonal co-therapy in 6 of 7 patients, prescribed at 2.5 mg orally daily, continued for all 28 days of the 28-day cycle. Given prior letrozole intolerance, fulvestrant was used as the hormonal co-therapy in one patient, dosed at 500 mg intramuscularly on days 1 and 15 of the 28-day cycle.

Dose reductions for palbociclib were made in 3 of 7 patients, initially to 100 mg on the same cyclic schedule (two due to grade 3–4 neutropenia, one due to grade 2 stomatitis). One of these patients experienced recurrent grade 4 neutropenia and was further dose reduced to 75 mg days 1–21, then 75 mg days 1–14 of the 28-day cycle, then switched to abemaciclib as an alternative CDK4/6 inhibitor. Abemaciclib was initiated at 50 mg oral for days 1–21 of the 28-day cycle and up-titrated to 150 mg with the same cyclic dosing, as tolerated by the patient. One patient stopped therapy without dose reduction after 7 cycles at her request due to grade 3 fatigue. The most common adverse effect of treatment was neutropenia, reported overall in 5 of 7 patients. Fatigue was reported in 3 patients, nausea in 3 patients, and arthralgia/myalgia in 2 patients.

Outcomes of CDK4/6 inhibitor and hormonal combination therapy are described in Table 2. Among the 7 patients, six had some decline in inhibin A and/or B levels during treatment (see Fig. 1), three had confirmation of partial disease response on imaging, and two others had

Table 1
Baseline clinical and tumor characteristics of patients with recurrent granulosa cell tumor of the ovary treated with Cyclin-Dependent Kinase (CDK) 4/6 inhibitors in combination with hormonal therapy.

Patient	Age at diagnosis (years)	Stage at diagnosis	Prior Treatment*			CDK4/6 inhibitor	Co-therapy	Years since diagnosis	Metastatic disease at start of treatment
			Surgery (N)	Radiation (Pelvic)	Systemic (N lines)				
1	28	Unstaged	13	Yes	5	Palbociclib	Letrozole	36	Chest/lungs, liver, lymph nodes
2	48	Stage IC	4	Yes	6	Palbociclib	Letrozole	24	Pelvic masses
3	37	Stage II	1	No	14	Palbociclib	Letrozole	8	Liver, lymph nodes, spleen
4	50	Stage IC	3	No	2	Palbociclib -> abemaciclib	Letrozole	8	Pelvic masses
5	27	Stage II	6	No	8	Palbociclib	Letrozole	17	Carcinomatosis, lymph nodes
6	53	Unstaged	3	Yes	5	Palbociclib	Fulvestrant	13	Abdominal/pelvic masses
7	37	IA	3	No	1	Palbociclib	Letrozole	5	Carcinomatosis

*See Table S1 for additional details.

Table 2
Clinical outcomes of patients with recurrent granulosa cell tumor of the ovary treated with Cyclin-Dependent Kinase (CDK) 4/6 inhibitors in combination with hormonal therapy.

Patient	28-day cycles of treatment (N)	Best response to treatment	Dose reductions (N)	Time to discontinuation (weeks)	Reason for discontinuation	Overall Survival* (months)	Vital status
1	3	–	–	12.3	Progression	16.0	Deceased
2	8†	–	–	44.3	Progression	35.1	Deceased
3	20	Partial response	–	80	Progression	89.4+	Alive without disease
4	22†	Partial response	4‡	106+	–	61.8+	Alive with disease
5	30	Partial response	1	118.6+	–	69.2+	Alive with disease
6	8	Stable disease	–	31.4	Grade 3 fatigue	62.1+	Alive without disease
7	16	Stable disease	1	64.6+	–	37.7+	Alive with disease

* Survival since initiation of CDK4/6 inhibitor treatment.
† Treatment interruptions due to COVID and bowel obstruction (patient 2) and treatment toxicity (patient 4) led fewer total cycles on treatment than 28 day periods on treatment, see Fig. 1 for details of treatment interruption timing.
‡ Palbociclib dose reduced x3, then switched to abemaciclib due to persistent neutropenia.
+ Denotes the patient remained on treatment or alive at the time of data cutoff June 30th, 2023.

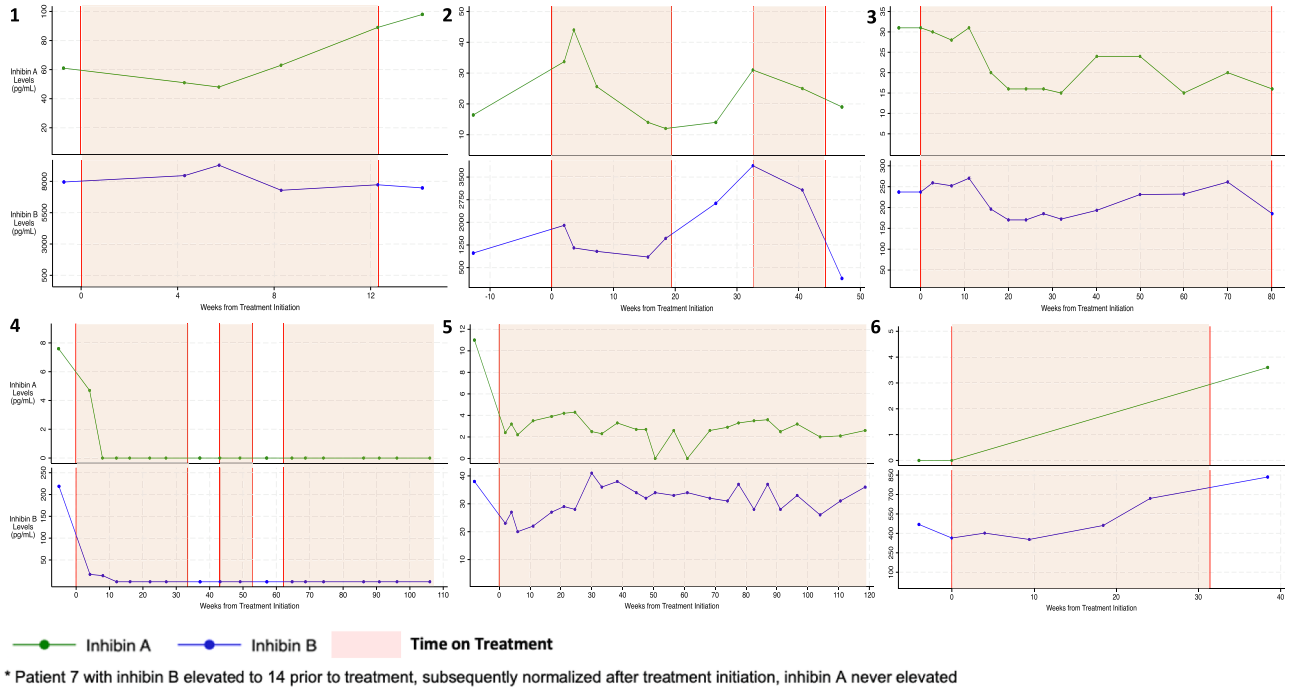

Fig. 1. Patient-level trends of inhibin A and B during treatment with Cyclin-Dependent Kinase (CDK) 4/6 inhibitors in combination with hormonal therapy in patients with recurrent granulosa cell tumor of the ovary.* Patient 7 with inhibin B elevated to 14 prior to treatment, subsequently normalized after treatment initiation, inhibin A never elevated.

imaging confirmed stable disease. Three patients progressed on therapy, one discontinued therapy due to toxicity, and three remained on therapy as of the cutoff for data collection on June 30th, 2023. The median duration of time on this treatment regimen and median overall survival were not reached at the time of data cutoff. At this date, 3 patients remained on therapy (current median duration on treatment of 64 weeks and counting, range 12–118 weeks) and 5 patients were alive (current median survival since treatment initiation of 62 months, range 16–89 months).

Two patients never had imaging confirmed evidence of clinical benefit to the CDK4/6 inhibitor and hormonal therapy regimen. One (patient 1) rapidly progressed within 3 cycles and died just over 3 months after treatment discontinuation. The other (patient 2) was treated for 4 cycles prior to holding treatment due to COVID-19 infection, then subsequent small bowel obstruction, at which time a CT scan showed increased size of a pelvic mass. Given she had been off treatment for 3 months at the time of the scan, therapy was restarted upon resolution of the bowel obstruction. However, she showed progression soon thereafter. Therapy was discontinued at this time and she died less than 4 months later.

The other 5 patients showed at least stable disease on interval imaging. All remained alive, and three remained on CDK4/6 inhibitor and hormonal therapy as of the data cutoff on June 30th, 2023. Patient 3 discontinued this treatment due to disease progression after 16 cycles. She was switched to bevacizumab and oral cyclophosphamide for 4 cycles with further progression. At this point the patient elected to undergo cytoreductive surgery, with successful resection to no gross residual disease. Patient 6, who stopped treatment after 7 cycles due to

grade 3 fatigue, subsequently underwent radiation to a psoas muscle lesion, followed by a successful cytoreductive surgery to no gross residual disease of abdominal/pelvic masses. Among the remaining three patients, two continued on palbociclib and one on abemaciclib in combination with letrozole at the time of data collection. Patient 4 had continued response in shrinkage of pelvic masses at last imaging after 16 cycles of therapy. Patient 5 had stable pelvic masses after initial partial response, after 22 total cycles of therapy. Patient 7 had stable carcinomatosis at last imaging after 3 cycles of therapy.

4. Discussion

In this case series of seven patients, therapy with a CDK4/6 inhibitor and hormonal therapy led to partial responses in three patients and stable disease in two patients. All were heavily pre-treated with median of three prior cytoreductive surgeries and 6 prior lines of therapy. Median duration of treatment and overall survival were not reached with 3 patients remaining on therapy and 5 alive at data cutoff. The regimen was well tolerated, although neutropenia was commonly encountered; toxicity required dose reductions in three patients and one patient discontinued therapy.

A small series like ours has both merits and limitations. The strengths include these cases may represent a starting point for further research. Granulosa cell tumors are relatively rare, making trial accrual challenging, and we provided detailed clinical information so others may consider this treatment approach. Limitations include limited generalizability and scope given the small numbers and selection bias inherent to these types of reports.

CDK4/6 inhibitors (palbociclib, ribociclib, and abemaciclib) improves survival relative to endocrine monotherapy in HR-positive advanced breast cancer (Finn et al., 2016; Finn et al., 2022; Hortobagyi et al., 2018; Hortobagyi et al., 2022; Tripathy et al., 2018; Lu et al., 2022; Goetz et al., 2022). The choice among these agents is often driven by provider preference and toxicity profiles. Palbociclib and ribociclib may increase rates of neutropenia, and abemaciclib increases risk of diarrhea. Ribociclib may also increase liver function tests and lead to QTc prolongation. No trial has compared agents to each other, but in one *meta*-analysis, there was no significant difference among the CDK4/6 inhibitors (Giuliano et al., 2019).

The benefit of CDK4/6 inhibitors are currently being evaluated in clinical trials for patients with gynecologic cancers. Given the rarity and indolent nature of granulosa cell tumor of the ovary, the benefit of the addition of CDK inhibitors to hormonal therapy may be challenging to observe. In a phase 2, open-label, single-arm trial enrolling 51 patients with recurrent low grade serous ovarian carcinoma, patients received ribociclib and letrozole for 3 weeks of a 28-day cycle until disease progression (Slomovitz et al., 2023). Of 48 patients included in the analysis, 38 (79 %) patients obtained clinical benefit. In another phase II trial, patients with estrogen receptor positive advanced/recurrent endometrial cancer were randomized to receive letrozole with palbociclib or placebo. Among 77 patients, letrozole with palbociclib significantly improved progression-free survival versus letrozole alone (median 8.3 vs. 3.0 months) (Mirza et al., 2020). Several other clinical trials and case reports have reported activity in patients with gynecologic cancers (Colon-Otero et al., 2020; Frisone et al., 2020; Konecny et al., 2016; Coffman et al., 2022), and several clinical trials are ongoing (NCT04469764, NCT04393285) (Konstantinopoulos et al., 2023).

5. Conclusion

Granulosa cell tumor of the ovary is an uncommon disease that tends to be relatively resistant to traditional systemic therapies. CDK4/6 inhibitors, in combination with antiestrogen therapy, represent a targeted therapy strategy that has proven activity in HR-positive breast cancer, with additional indications under active exploration for HR-positive gynecologic cancers. We have presented a case series of seven heavily pre-treated patients with recurrent granulosa cell tumor of the ovary, demonstrating activity as a possible treatment strategy in this indolent disease with unmet need for novel treatment options warranting further prospective investigation.

6. Consent

This project was approved by the Duke University Institutional Review Board. Given that the project involved a retrospective case series with chart review and extraction of de-identified and non-identifiable patient data, consent from individual patients was not required by the IRB as a part of the approval.

CRediT authorship contribution statement

Benjamin B. Albright: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Software, Visualization, Writing – original draft, Writing – review & editing. **Stephanie Shuey:** Conceptualization, Data curation, Investigation, Writing – review & editing. **Angeles Alvarez Secord:** Conceptualization, Supervision, Writing – review & editing. **Laura J. Havrilesky:** Conceptualization, Supervision, Writing – review & editing. **Andrew Berchuck:** Conceptualization, Supervision, Writing – review & editing. **Rebecca A. Previs:** Conceptualization, Investigation, Methodology, Resources, Project administration, Supervision, Writing – original draft, Writing – review & editing.

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.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.gore.2023.101297.

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