Case report

Palbociclib in the treatment of recurrent ovarian cancer

Dai Wee Lee⁎, Gwo Fuang Ho
Clinical Oncology Department, University Malaya Medical Center, Malaysia

ARTICLE INFO

Keywords:
Ovarian cancer
Palbociclib
CDK4/6 inhibitor

ABSTRACT

Serous ovarian cancers are typically high grade and recur within a short interval. The currently available therapeutic options provide a relatively low response rate and the progress-free survival are short-lived. There is emerging data that CDK4/6 may be effective in metastatic ovarian cancer. This case describes the use of palbociclib after multiple lines of cytotoxic chemotherapy and hormonal therapy. At 30 months upon commencement of palbociclib and letrozole, this patient continues to respond to the treatment radiologically and in the suppression of CA125.

1. Introduction

Serous ovarian cancer accounts for 80% of ovarian cancer, most of them being high grade (Ledermann et al., 2013). Traditionally, the expected survival for recurrent ovarian cancer is less than 12 months (Ledermann et al., 2013). The management of relapsed disease is dependent on the duration that has elapsed since completion of platinum-based chemotherapy and the time of relapse i.e. the platinum-free interval (PFI). Patients with a PFI of 6 months or longer are considered to have platinum-sensitive disease and often respond to platinum-base chemotherapy during the relapse. Patients with PFI of 6 months or less are deemed platinum-resistant. This group also includes platinum-refractory disease, in which patients progress while on platinum-based chemotherapy. In the platinum resistant setting, conventional chemotherapy such as paclitaxel, pegylated liposomal doxorubicin, topotecan, and gemcitabine give rise to progression-free survival of 3–4 months, with an overall response rate of less than 15% (Ledermann et al., 2013).

Cyclin-dependent kinase (CDK) is a key driver in cell division. CDK activities largely define the phases of the cell cycle, while changes in CDK activity dictate transitions between the cell cycle phases (Tannock et al., 2013). Among the CDK family, CDK 4 and CDK 6 play a vital role in the transition from G1 to S phase (Tannock et al., 2013).

The development of CDK 4/6 inhibitors is based on the action of binding to CDK 4 and 6 ATP pocket, which leads to a substantial inactivation of Cyclin D-CDK4/6 complexes. This subsequently leads to an increase in the activity of phosphorylated Rb. The logical consequence is a G1 phase arrest. Eventually, cell apoptosis will occur in tumor cells.

CDK 4/6 inhibitors have been evaluated in pre-clinical studies in approximately 30 different cancers (Agghar et al., 2015). Among all cancer types, development in estrogen receptor positive metastatic breast cancers has been the most robust with 3 compounds approved in recent years i.e. palbociclib, ribociclib, and abemaciclib as a single agent or in combination with hormonal therapy. The rationale of CDK 4/6 inhibitor in combination with estrogen suppression is largely supported by preclinical studies that identified a dependence of hormone receptor positive breast cancer on CDK4 and CDK6 signalling and a synergistic effect from targeting the ER, cyclin-D–CDK4/6–Rb pathway (Finn et al., 2009).

An in vitro study by Konecny at al have demonstrated responses to CDK4/6 inhibition in approximately half of 40 ovarian cancer cell lines (Konecny et al., 2011). There is an ongoing phase II trial investigating palbociclib in recurrent ovarian cancer with Rb-proficiency and low p16 expression. The interim analysis has shown tolerable toxicity profile and radiological median progression-free survival of 3.7 months and Gynecologic Cancer InterGroup CA125 criteria median progression-free survival of 4.0 months (Konecny et al., 2016).

Besides palbociclib, another CDK4/6 inhibitor, ribociclib has also been explored in gynecological malignancies. A phase 2 trial by Colon-Otero et al treated patients with relapsed estrogen-receptor positive ovarian and endometrial cancers. Among the 20 patients with ovarian cancer, this trial reported 50% progression-free survival at 12 months, and a similar 55% for endometrial cancer. (Colon-Otero et al., 2019)

Therefore CDK4/6 inhibitors used alone or as combination therapies could be potentially useful in recurrent ovarian cancer. We report a case of recurrent ovarian cancer treated with palbociclib and letrozole.

2. Case

Madam X was initially diagnosed with stage 3 ovarian cancer in
1994 at 25-years-old. She underwent a total abdominal hysterectomy, bilateral salpingo-oophorectomy and infracolic omentectomy followed by 6 cycles of adjuvant carboplatin AUC 5 and paclitaxel 175 mg/m². She remained disease free for 19 years until 2013.

In 2013, at 44-years-old, she presented with left pleural effusion which was confirmed to be recurrent papillary serous carcinoma by pleuroscopy and cytology. She received combination carboplatin, paclitaxel, and bevacizumab for 8 months and stopped in view that the patient opted for a drug holiday. The radiological and biochemical response was unclear as patient was treated in another oncology centre.

In 2016, her pleural effusion worsened and she was transferred to our centre. At this juncture, BRCA testing was done and found no BRCA1/2 mutation. In view of the long relapse-free interval, she was deemed platinum-sensitive. Thus she was treated with carboplatin AUC5 and pegylated liposomal doxorubicin 30 mg/m² q3w for 6 cycles. Her pleural effusion improved clinically and radiologically. There was no measurable disease at that point.

After 5 months, in April 2017, she presented with left axillary lymphadenopathy. Core biopsy of the axillary lymph node showed high-grade serous carcinoma with the following immunohistochemistry findings: estrogen receptor positive, progesterone receptor negative, HER2 negative, PD-L1 expression 0%, and microsatellite instability (MSI) negative. At this juncture, patient was deemed to be platinum resistant, thus non-platinum treatment options were explored. Patient also expressed wishes to have oral treatment. She was then commenced on letrozole 2.5 mg OD.

In May 2017, her CA125 was increasing from 55U/mL to 77U/mL, and letrozole was changed to tamoxifen 20 mg OD. However, CA125 continued to rise to 113U/mL within a month. Her performance status was ECOG 0. She was then commenced on palbociclib 125 mg OD 3 weeks on and 1 week off schedule in combination with letrozole 2.5 mg OD since June 2017. Figures 1 and 2 show the radiological and biochemical responses with this treatment regimen. She tolerated palbociclib well throughout the treatment and did not require any dose adjustments or dose delays. The adverse events reported were grade 2 leukopenia and grade 2 neutropenia. CA125 remained to respond for 30 months and she is still ongoing treatment.

3. Discussion

Following two lines of systemic chemotherapy and two lines of hormonal therapy, this patient showed a prolonged response to palbociclib and letrozole. To the best of our knowledge, no similar clinical case in which such prolonged progression-free survival has been reported.

Olaparib, a PARP inhibitor has shown improvement in progression-free survival in the SOLO-2 trial for BRCA 1/2 mutation recurrent ovarian cancer (Pujade-Lauraine et al., 2017). Thus, the option of olaparib was explored however this patient was found to have a normal BRCA gene.

Her disease was resistant to two lines of hormonal therapy however responded well to the combination of CDK4/6 inhibition and aromatase inhibition. This may suggest CDK4/6 deregulation causing endocrine resistance as observed in estrogen receptor positive breast cancer. Biomarker may be the key in the selection of patients that may respond to CDK4/6 inhibitors. A similar case reported by Frisone et al identified a case of ovarian cancer with homozymous CDKN2A deletion that responded for 12 months to palbociclib and letrozole (Frisone et al., 2020).

The progression-free survival observed is beyond 30 months. The disease response by radiological means according to RECIST criteria was a partial response. According to the Gynecologic Cancer InterGroup CA125 criteria, she achieved a 50% reduction of CA125 at 3 months upon started palbociclib and letrozole, which continues to sustain.

The adverse events observed were leucopenia and neutropenia as expected as class effects of CDK 4/6 inhibitors. Since the adverse events were at most grade 2, no dose adjustments and dose delays were required. Management of adverse events was according to the PALOMA-2 trial for breast cancer (Finne et al., 2016).

4. Conclusions

In this case, palbociclib and letrozole have shown a prolonged progression-free survival of more than 30 months and an excellent toxicity profile. This could present a potential therapeutic role of CDK4/6 inhibition in recurrent ovarian cancers.

Consent for publication

Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal on request.

Author contribution

Dai Wee Lee wrote the work and Gwo Fuang Ho contributed to the revision of the work and gave the final approval of the version to be.
published. All authors read and approved the final manuscript.

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

Asghar, U., Witkiewicz, A.K., Turner, N.C., et al., 2015. The history and future of targeting cyclin-dependent kinases in cancer therapy. Nat. Rev. Drug Discov. 14, 130–146.

Colon-Otero, G., Weroha, S.J., Zanfagnin, V., Foster, N.R., Asmus, E., Hendrickson, A.E., et al., 2019. Results of a phase 2 trial of ribociclib and letrozole in patients with either relapsed estrogen receptor (ER)-positive ovarian cancers or relapsed ER-positive endometrial cancers. J. Clin. Oncol. 37 (15), 5510.

Finn, R.S., Dering, J., Conklin, D., et al., 2009. PD 0332991, a selective cyclin D kinase 4/6 inhibitor, preferentially inhibits proliferation of luminal estrogen receptor-positive human breast cancer cell lines in vitro. Breast Cancer Res. 11 R77-R77.

Finn, R.S., Martin, M., Rugo, H.S., Jones, S., Im, S.A., Gelmon, K., et al., 2016. Palbociclib and letrozole in advanced breast cancer. N Engl. J. Med. 375, 1925–1936.

Frisone, D., Charrier, M., Clement, S., Christnat, Y., Thouvenin, L., Hamicsko, K., et al., 2020. Durable response to palbociclib and letrozole in ovarian cancer with CDKN2A loss. Cancer Biol. Ther. 21 (3), 197–202.

Konecny, G.E., Winterhoff, B., Kolarova, T., Qi, J., Manivong, K., Dering, J., et al., 2011. Expression of p16 and retinoblastoma determines response to CDK4/6 inhibition in ovarian cancer. Clin. Cancer Res. 17, 1591–1602.

Konecny, G.E., Hendrickson, A.E., Jatoi, A., Burton, J.K., Parody, J., Gluspy, J.A., et al., 2016. A multicenter open-label phase II study of the efficacy and safety of palbociclib a cyclin-dependent kinases 4 and 6 inhibitor in patients with recurrent ovarian cancer. J. Clin. Oncol. 34 (15_suppl), 5557.

Ledermann, J.A., Raja, F.A., Fotopoulou, C., Gonzalez-Martín, A., Colombo, N., Sessa, C., et al., 2013. Newly diagnosed and relapsed epithelial ovarian carcinoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann. Oncol. 24 Suppl 6 vi24-32.

Pujade-Lauraine, E., Ledermann, J.A., Selle, F., Gembki, V., Passon, R.T., Oza, A.M., et al., 2017. Olaparib tablets as maintenance therapy in patients with platinum-sensitive, relapsed ovarian cancer and a BRCA1/2 mutation (SOLO2/ENGOT-Ov21): a double-blind, randomised, placebo-controlled, phase 3 trial. Lancet Oncol. 18 (9), 1274–1284.

Tannock, I.F., Hill, R.P., Bristow, R., Harrington, L., et al., 2013. The Basic Science of Oncology, 5th Ed. McGraw-Hill, New York.