中文題目：荷爾蒙陽性乳癌病人使用 CDK4/6 抑制劑 palbociclib 造成白血球低下暨腹膜透析病藥物動力學分析

英文題目：Real world experience of CDK4/6 inhibitor palbociclib associated neutropenia in a hormone positive breast cancer cohort and pharmacokinetics study in a patient with peritoneal dialysis

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Background: The development of CDK4/6 inhibitors (including palbociclib, abemaciclib, ribociclib) has revolutionized the treatment landscape of hormone positive (HR(+)) metastatic breast cancer patients. CDK4/6 inhibitors are well tolerated and offer a substantial chemotherapy free period that significantly improves patient quality of life. However, the most significant adverse effect is neutropenia, which can be dose limiting and requires constant monitoring in patients. To understand the impact of palbociclib associated neutropenia on patient outcome, we conducted this study.

Methods: This retrospective study enrolled 94 patients with treatment-naïve HR(+) metastatic breast cancer from 2017-2020 who received the CDK4/6 inhibitor palbociclib as first line treatment at VGHTPE. The incidence and patterns of neutropenia were analyzed. Prognostic factors were analyzed by the Cox proportional hazards model. In addition, we quantified the concentration of palbociclib in a patient undergoing peritoneal dialysis who had dose reduction due to neutropenia. The concentrations of palbociclib in peritoneal fluid and serum in this patient were measured by LC-MS.

Results: A total of 94 patients with HR(+) metastatic breast cancer (mBC) was enrolled. All patients were female, with 87% postmenopausal, and 38% de novo mBC. 45 patients received palbociclib as 1st line treatment. In all the patients enrolled, 37 patients had best response as complete or partial response (CR, PR), 43 had stable disease (SD), and 9 had progressive disease (PD). In the patients who received 1st line treatment, both the progression free survival (PFS) and overall survival (OS) were not reached (median follow up time: 20.2 months), and the objective response rate (ORR) was 51.1%. The rate of all grade and grade 3/4 neutropenia were 96.8 and 76.6, respectively. Univariate analysis revealed BMI <19 (p=0.001), presence of lung metastases (p=0.034), and presence of liver metastases (p=0.007) as risk factors for grade 3/4 neutropenia. Multivariate analysis revealed low BMI and presence of liver metastases to be significantly associated with development of neutropenia. 50% of the patients reached lowest neutrophil count in the first 2 cycles (day 1-day 56), defined as early neutropenia. Early neutropenia patients had a significantly shorter PFS compared to patients who developed neutropenia after day 56 (PFS 306

days versus 581 days, p=0.0013).

We report a 65 y/o patient with peritoneal dialysis who received palbociclib use due to metastatic HR(+) breast cancer. She was started with 125mg, but developed severe neutropenia on day 17 after use, and palbociclib was temporarily discontinued. After 15 days of discontinuation, neutrophil count normalized and she was restarted on 100mg daily. Peritoneal dialysate fluid was collected during when she was using 125mg and 100mg, as well as serum samples. Palbociclib concentration was quantified by mass spectrometry. By analyzing palbociclib concentration at various time points, several observations could be made: 1. Palbociclib levels in peritoneal dialysate ranged from around 20-50 ppb during on-drug treatment and did not vary substantially during treatment of 100mg or 125mg. Palbociclib levels decreased to undetectable state during drug discontinuation. 2. Serum levels of palbociclib was around 100-110 ppb during drug administration and <10ppb during discontinuation. The serum levels did not differ significantly at during treatment of 100mg or 125mg. The results demonstrated that an unexpectedly high level of palbociclib was present in the peritoneal fluid. Also, the serum palbociclib levels were not significantly different between when using 125mg or 100mg.

Conclusions: In our cohort, a high proportion of patients (76.6%) hade grade 3/4 neutropenia when using palbociclib. Low body weight and presence of liver metastases were significantly associated with incidence of grade 3/4 neutropenia on palbociclib. Early development of neutropenia nadir was significantly associated with worse outcome. Our case study demonstrated that a high palbociclib concentration could be quantified in the peritoneal fluid, and dose reduction of palbociclib did not serially affect the peak values of serum levels. Besides providing real world data on palbociclib associated neutropenia, our study reported the first quantification of palbociclib in peritoneal dialysis fluid and provides significant insight in palbociclib real world use.