Real-world relative dose intensity in patients with advanced or metastatic breast cancer treated with cyclin-dependent kinase (CDK) 4/6 inhibitors in Sweden

RWD9

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Introduction

CDK4/6 inhibitors for the treatment of hormone receptor (HR) positive / human epidermal growth factor receptor 2 (HER2) negative advanced breast cancer (aBC) are well established in Sweden. In the Swedish setting, there are differences in the strength of individual tablets/packages and pricing of the currently available CDK4/6 inhibitors (ribociclib, palbociclib and abemaciclib). To manage possible adverse effects and/or to maintain adherence, treatment with CDK4/6 inhibitors is subject to dose adjustments (Table 1). Treatment effect is not compromised by downward dose modifications [1] [2], which could lead to cost savings.

Objectives

Evaluate real-world relative dose intensity (RDI) and drug-holiday-RDI (dhRDI) in patients with HR+/HER2- aBC treated with ribociclib, palbociclib or abemaciclib in Sweden.

Table 1. Recommended dose modification for adverse reactions with CDK4/6 inhibitors.

	Starting dose	1. adjustment	2. adjustment
Ribociclib [3]	600 mg/day	400 mg/day	200 mg/day
Palbociclib [4]	125 mg/day	100 mg/day	75 mg/day
Abemaciclib [5]	300 mg/day	200 mg/day	100 mg/day

Methods

Based on Swedish national prescription data, an observational registry-based analysis was carried out. Data was extracted from the Prescribed Drug Register based on ATC code including all patients who received at least one prescription of a CDK4/6 inhibitor treatment between 01/2016 and 03/2022. As CDK4/6 inhibitor treatment became more established in 2018, only patients who initiated treatment from 2018 onwards were included in the analysis. Patients with more than one CDK4/6 inhibitor treatment had their later CDK4/6 inhibitor treatments excluded. Patients with treatment interruption by another CDK4/6 inhibitor or who initiated treatment with a new CDK4/6 inhibitor within 180 days of last purchase were excluded. Exclusions were performed for sake of homogeneity of comparison between CDK4/6 inhibitor treatments.

To capture real-world consumption, no exclusion criteria was set for exceeding maximum Summary of Product Characteristics (SPC) [3] [4] [5] recommended dosing. Total dose was defined as total milligrams received. Treatment duration was calculated from index date, defined as date of first purchase until last purchase +14 days. 14 days were added as patients were assumed to progress and/or discontinue treatment on average midway through a treatment cycle. RDI for each CDK4/6 inhibitor was defined by dividing total milligrams administered with total days treated, multiplied by the defined daily dose (DDD) per the SPC (Figure 1). dhRDI was defined as RDI without down-dosing and calculated as total number of purchases, divided by total days treated, divided by SPC defined treatment cycle length (Figure 1). For dhRDI, every recorded purchase is assumed to correspond to a single treatment cycle. dhRDI aims to capture the size of the effect that treatment cycle related off treatment periods have on RDI.

Figure 1. Calculation methods for RDI and dhRDI.

$$RDI = \frac{total\ miligrams\ administered}{total\ days\ treated\ \times recommended\ SPC\ posology}$$

$$dhRDI = \frac{total\ number\ of\ purchases}{total\ days\ treated\ /\ treatment\ cycle\ length}$$

Table 2. Patients by year of initiation, total patients treated and excluded treatments.

	2018	2019	2020	2021	2022	Total	Excluded
Ribociclib	79	231	184	152	24	670	152
Palbociclib	506	387	388	464	66	1811	351
Abemaciclib	0	15	28	42	6	91	96

Results

2572 patients who had received at least one prescription of a CDK4/6 inhibitor were included in this analysis (Table 2) (ribociclib: 670; palbociclib: 1811; abemaciclib; 91). Mean time on treatment (ToT) was 16.0, 15.4 and 14.1 months for ribociclib, palbociclib and abemaciclib, respectively (Table 3). Average total RDI was 0.80, 0.83 and 0.82 and average total dhRDI was 0.92, 0.97 and 1.00 for ribociclib, palbociclib and abemaciclib, respectively (Table 3). The findings are in line with results from clinical trials (Table 4).

Table 3. Results for average total RDI, average total dhRDI and mean ToT from this analysis.

	Average total RDI	Average total dhRDI	Average dose (mg)	Mean ToT (months)
Ribociclib	0.80	0.92	479.95	16.03
Palbociclib	0.83	0.97	103.76	15.39
Abemaciclib	0.82	1.00	245.44	14.15

Table 4. RDIs and estimated dhRDIs from clinical trials by combination partner.

	Mean RDI + Letrozole	Mean dhRDI + Letrozole	Mean RDI + Fulvestrant	Mean dhRDI + Fulvestrant
Ribociclib	0.81 [9]	0.95 * [9]	0.85 [10]	0.93* [10]
Palbociclib	0.87 [11]	0.93* [11]	0.86 [12]	n.a.
Abemaciclib	0.79 [13]	n.a.	0.87 [14]	n.a.

*Estimated

Discussion and limitations

Ribociclib packages contain the same tablet strength regardless of dose, and dosing is adjusted according to the number of tablets taken per day. Ribociclib treated patients that require dose adjustment are able to complete their treatment cycle with the adjusted dose by using already purchased tablets (3 → 2 → 1 tablet(s) per day). Palbociclib and abemaciclib tablet strengths correspond to daily dose, thus dose adjustments are made by changing to a different package size. The ability to use previously prescribed tablets after down-dosing may reduce drug wastage and therefore lower the dhRDI. The dataset contains variations in purchasing frequency and volume across patients treated with ribociclib. This may be a confounding factor when estimating dose adjustments, RDI and length of treatment, and the actual RDI for ribociclib patients may therefore differ slightly from the presented estimations. All estimations are anchored in SPC recommended posology and treatment cycle duration.

Ribociclib and abemaciclib have been available as treatment options for a shorter period of time than palbociclib (reimbursed from 2/2018 [6], 7/2019 [7] and 7/2017 [8], respectively). As such the number of patients exposed to said treatments (and available follow-up) is significantly lower than to palbociclib. Furthermore, possible comorbidities, combined therapies and lines of treatment cannot be derived from the available data and all estimations are based on total pooled population.

These factors may have an effect on estimated mean times on treatment and RDI. As such, they should not be used as surrogate endpoints for efficacy or clinical effect. It was not possible to adjust for any of the limitations above, as only prescription data was analyzed and access to medical records that could explain deviations from recommended posology was not available.

This analysis includes all HR+/HER2- aBC patients treated with a CDK4/6 inhibitor in Sweden between 01/2018 and 03/2022. Reported RDIs and dhRDIs describe total drug usage and time on treatment for all patients, and as such actual RDIs observed in Sweden.

Conclusion

Dosing adjustments of CDK4/6 inhibitors used to treat HR+/HER2- aBC patients in Sweden appear to reflect RDIs observed in randomized clinical trials. This provides an opportunity for real-world treatment cost savings if the pricing of CDK4/6 inhibitors is linear to the administered dose.

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Keywords

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Author disclosure

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