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ORIGINAL RESEARCH

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Real-world analysis of the economic and therapeutic burden in advanced breast cancer patients in Italy

Simona Palladino[a], Valentina Perrone[b], Elisa Giacomini[b], Diego Sangiorgi[b], Eleonora Premoli[a], Diletta Valsecchi[a], Luca Degli Esposti[b] and Matteo Basilio Suter[a]

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ABSTRACT

Background: This real-world analysis evaluated drug utilization focusing on wastage and healthcare costs for treatment of patients with advanced breast cancer (aBC) hormone receptor-positive (HR+)/human epidermal growth factor receptor-2 negative (HER2-) in Italy.

Methods: A retrospective analysis was conducted on administrative data covering about 13.3 million health-assisted individuals. Across January/2017–June/2021, all patients with HR+/HER2-aBC were identified by ≥ 1 prescription for cyclin-dependent kinase 4/6 inhibitors (CDK 4/6i). Cost analysis was performed and updated referring to the prices of November 2021.

Results: Overall, 3,647 HR+/HER2-aBC patients were included (2,627 palbociclib treated, 729 ribociclib treated, and 291 abemaciclib treated). After 12 months of follow-up, 35% of palbociclib patients had a dose reduction (on average 8.9 wasted pills/patient), 44.7% of abemaciclib patients had a dose reduction (on average 6.7 wasted pills/patient), 22.1% of ribociclib patients had a dose reduction (no wasted pills). Therapy wastage added up to 528,716€ for palbociclib-treated patients (524€/patient) and 5,738€ in abemaciclib-treated patients (151€/patient). No wastage was attributed to ribociclib.

Conclusions: Dose reduction was associated with drug wastage in palbociclib and abemaciclib-treated patients, but not in ribociclib-treated ones. These findings might be helpful to policy decision-makers who, for healthcare strategies implementation, among several variables should consider the possible restraining of drug wastage.

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Advanced breast cancer; cyclin-dependent kinase 4/6 inhibitors; real-world evidence; dose reduction; drug wastage; healthcare cost analysis

1. Introduction

In the era of rising healthcare costs and limited resources, drug wastage evaluation could be helpful for health systems and payers to reduce costs significantly. Discarding unused medications is a public issue affecting all therapeutic areas, especially oncology. During 2018, the total cost of cancer (direct costs including cancer drugs, informal care costs, indirect costs) in Europe was €199 billion, of which healthcare expenditures were €103 billion with €32 billion for oncologic medications [1]. Thus, when a portion of those drugs is discarded after being partially used or discontinued, the cost of that wastage can be considerable. In 2008, Fasola and colleagues reported that in their Department of Medical Oncology in Italy, by comparing prescription orders with the actual amounts of consumed drugs, the net loss from drug wastage was 6.4% of the department's total expenditure [2]. In 2014, the same group estimated that drug wastage accounted for 8.3% of the Department's annual drug expenditure and over 70% of these costs were attributable to six drugs (cetuximab, docetaxel, gemcitabine, oxaliplatin, pemetrexed and trastuzumab) [3]. A report on the top 20 oncology-infused drugs in the United States showed that, based on 2016 projected sales, the leftover drugs after treatment ranged from 1% to 33%, and this large variability was due to market volumes and vial sizes [4]. Despite infused anticancer drugs have been a focus of attention in terms of wastage, the estimation of economic burden from drug wastage for orally administered anticancer drugs has been poorly investigated and represents an important component of cancer care and costs.

According to the most recent global cancer burden data released by the World Health Organization (WHO), breast cancer (BC) is the most prevalent cancer worldwide, with almost 2.26 million new cases in 2020 [5] and with approximately 55,000 new diagnosed cases per year in Italy [6]. Hormone receptor-positive (HR+)/human epidermal growth factor receptor-2 negative (HER2-) BC represents approximately 70% of BCs [7,8]. While most of BCs are detected in early stages, about 30% of them eventually develop into advanced BC (aBC) [9]. The management of HR+/HER2- aBC patients is based on first-line treatment with a novel class of orally administered agents acting as inhibitors of cyclin-dependent kinase 4 and 6 (CDK 4/6i), namely palbociclib (approved by the EMA in 2015), ribociclib and abemaciclib (approved by the EMA in 2017) [10]. Palbociclib is available as 21 or 63 tablets per package with three different dosages each (125 mg, 100 mg and 75 mg) [11]. Ribociclib is

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Article highlights

- Drug wastage is an unsolved issue for public health services and payers. This is particularly true in oncology area since the frequent necessity of progressing through therapeutic schemes or dose adjustments can cause a costly discard of unused medications.
- This real-world analysis assessed drug utilization and wastage in women with HR+/HER2- advanced breast cancer treated with CDK 4/6 inhibitors currently approved in Italy, namely palbociclib, ribociclib and abemaciclib. The economic analysis highlighted that the expenses for CDK 4/6 inhibitors were by far the weightiest cost item accounting for 65–75% of the overall healthcare expenditures.
- After one-year from the start of therapy with CDK 4/6 inhibitors, dose reductions were seen in 35% of women on palbociclib resulting in nearly 9 wasted pills per patient, 44.7% of those on abemaciclib resulting in average 6.7 wasted pills per patient, and 22.1% of those on ribociclib with no pill wastage. Discarding leftover drugs with dose adjustments occurs when the high dosage strengths prevent pill splitting and preservation for later use. The therapy with ribociclib did not imply wastage because this drug is available with a unique formulation of 200 mg, thus dosage can be modulated on the number of pills without requiring a new prescription.
- In the era of rising healthcare costs especially in the oncology setting, all strategies to keep drug wastage phenomenon under control are highly desirable. The data emerging from this analysis suggest that future efforts of pharmacological research should target dose strengths to facilitate dose adjustments and minimize until to cancel wastage of unused medications.

available as 200 mg tablets (63, 42, or 21 tablets per package) [12], while abemaciclib is dispensed as 28 tablets package in 3 strengths (150 mg, 100 mg, and 50 mg) [13]. The recommended posology for these medications is 125 mg for palbociclib, 600 mg for ribociclib and 300 mg for abemaciclib, administered for 21 days out of 28 for palbociclib and ribociclib and continuously for abemaciclib [11–14]. As for many oncology drugs, the dose of targeted therapies may need to be adjusted over time [15]. Indeed, the product labels of all three CDK 4/6i temporary specify that dose reduction, temporary interruption or discontinuation are required in the presence of adverse events/intolerance and other circumstances [11–13]. For palbociclib from the recommended dose of 125 mg/day, the first dose reduction is indicated to 100 mg/day, and the second to 75 mg/day, then permanent discontinuation is needed in case of further dose reduction below 75 mg/day [11]. Ribociclib dosage has to be lowered from the initial 600 mg/day (corresponding to 3 daily tablets 200 mg each), to 400 mg/day (2 daily tablets) as first reduction and 200 mg/day (1 daily tablet) as second reduction, if below the treatment has to be withdrawn [12]. For abemaciclib from the recommended dose of 150 mg twice daily, the first dose modification is indicated at 100 mg twice daily, and the second at 50 mg twice daily [13]. In clinical trials, dose reduction rates of palbociclib and ribociclib treatments have been found to be comparable, ranging from 36.0% to 36.1% [16,17]. A summary of the posology has been provided in Supplementary Table S1. Drug wastage may occur when a dose modification is needed but the dose cannot be split or saved for successive use [2,3,18]. This could be the case of palbociclib [19–21] and abemaciclib because of their available dosage strengths. Conversely, ribociclib dose adjustment could be achieved by changing the number of tablets assumed without recurring to a new prescription [21].

To provide a more complete characterization of the impact of dose modifications of palbociclib, ribociclib and abemaciclib, here we present an analysis based on real-world data captured by administrative claims database, describing dosing patterns and estimating the economic burden of the potential drug wastage associated with dose reductions in women with HR+/HER2- aBC treated with CDK 4/6i in Italy.

2. Methods

2.1. Data source

A retrospective analysis was conducted using administrative databases of a pool of Local Health Units, geographically distributed across Italy, covering about 13.3 million health-assisted individuals. These databases contain all data reimbursed by the Italia National Health Service (INHS), which is based on the principle of universal coverage of all residents. The following databases were used: (i) demographic database, which consists of all patient demographic data, such as gender, age, death; (ii) pharmaceuticals database, that supplies information on medicinal products reimbursed by the Italian national health system (INHS) as the Anatomical-Therapeutic Chemical (ATC) code, number of packages, number of units per package, unit cost per package and prescription date; (iii) hospitalization database, which encloses all hospitalizations data for patients under analysis, such as the discharge diagnosis codes classified according to the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM), Diagnosis Related Group (DRG) and DRG related charge (provided by the Health System); (iv) outpatient specialist service database, which incorporates all the information about visits and diagnostic tests date and type of prescription, description activity and laboratory test or specialist visit charge); (v) payment exemption database, which contains data of the exemption codes that allow to avoid the contribution charge for services/treatments when specific diseases are diagnosed. An anonymous univocal numeric code was assigned to each study subject to guarantee patients' data privacy, in full conformity with the European General Data Protection Regulation (GDPR) (2016/679). The patient code in each database permitted the electronic linkage among all databases. All the results coming out from the analyses were produced as aggregated summaries and never attributable to a single institution, department, doctor, individual, or individual prescribing behaviors. The analysis was conducted in compliance with the principles of the Declaration of Helsinki and approved by the local Ethics Committees of the Healthcare Departments involved. Informed consent was waived due to the use of encrypted anonymous data and to the retrospective nature of the research design.

2.2. Study design and study population

From January 2017 to June 2021, all aBC patients were identified by at least one prescription of CDK 4/6i (palbociclib, ATC code: L01XE33; ribociclib, ATC code: L01XE42; abemaciclib,

ATC code: L01XE50) and included in the retrospective observational analysis. Patients were allocated in three cohorts based on the drug first prescribed (palbociclib, ribociclib or abemaciclib). The index-date was defined as the date of the first drug prescription. Patients were characterized during all the available period before index-date and had at least 12 months of data availability after the index-date. The follow-up represents the treatment period. Moreover, patients subgrouped by menopausal status were included: in particular, premenopausal patients were identified by presence of at least one prescription for the following gonadotropin-releasing hormone (GnRH) analogues: leuprorelin (ATC code: L02AE02), goserelin (ATC code: L02AE03), triptorelin (ATC code: L02AE04). The prescription of GnRH analogues was used as proxy to detect premenopausal status as the three drugs listed above are approved for reimbursement by the INHS with the Note 51 of the AIFA (Italian Medicines Agency) for the treatment of estrogen receptor positive breast cancer in premenopausal women [22].

At index-date, mean and median age was evaluated and reported. During the treatment period (up to 12 months), drug usage in terms of daily mean dosage, number of dispensed drug packages, dose de-escalation (dose reduction) and mean wastage of pills per patients during dose de-escalation, were evaluated. Moreover, healthcare resource consumptions and related costs during the first year of follow-up were estimated and projected to the entire Italian population (patients with less of one year of follow-up due to death or loss of data availability were not computed in the analysis).

2.3. Drug utilization analysis

Drug utilization analysis was performed from treatment start up to 12 months and variables were evaluated every 3 months, in overall patients and those stratified by menopausal status. At each time point, the daily mean dosage of CDK 4/6i was calculated as the sum of total dosage prescribed during a prescription divided by the days covered by the prescription. The mean number of drug package dispensed during treatment was evaluated. The percentage of patients with dose de-escalation (reduction) was calculated based on the occurrence of dose reduction during treatment (evaluated on the posology of CDK 4/6i reported on the Summary of product characteristics SmPC). Drug wastage was defined as drug doses that could not be used by the patient following a dose reduction and calculated as the mean number of pills (units) wasted during dose reduction per patients. Since subsequent dose increase after a dose reduction was not observed in any of the clinical trials and the drug wastage was calculated based on drug reduction, it was not reported.

2.4. Healthcare resource consumption and cost analysis

During the first year of treatment, in alive patients, healthcare resource utilization was evaluated in terms of the following variables: (i) a mean number of CDK 4/6i drug prescriptions and of all other drugs (in terms of all drugs prescribed and reimbursed by the INHS), (ii) a mean number of hospitalizations, in terms of all-cause hospitalizations, and (iii) a mean number of outpatients specialists services prescribed and reimbursed by the INHS in terms of specialist tests and visits. The direct healthcare costs were evaluated over the treatment period and were related to the following resource consumption: hospitalizations (determined by using the DRGs tariffs), drug costs (evaluated for those drugs reimbursed by the INHS and using the INHS purchase price; costs for CDK 4/6i were reported according to current prices, November 2021 [14]). The outpatient specialist service costs were estimated accordingly to regional tariffs. Data were reported as the mean annual healthcare cost per patient. Moreover, the overall annual cost for therapy was evaluated among included patients. To estimate the total costs at National level, the number of patients in each treatment cohort was projected to the entire Italian population based on the census of the Italian Institute of Statistics for 2021 ($N = 59.236.213$); the overall annual cost related to wastage therapy among the study sample was also estimated and reproportioned to the entire Italian population.

2.5. Statistical analysis

Data are mostly reported descriptively. Continuous variables were presented as mean ± standard deviation (SD), categorical variables as numbers and percentages. Since costs are not normally distributed, to overcome the heteroscedasticity in the error variance of the cost data [23], a generalized linear model (GLM) was developed in order to evaluate the possible correlations between costs and the use of CDK 4/6i (considering palbociclib group as a reference due to its largest numerosity), adjusting for baseline variables: age, menopausal status, prescription of fulvestrant (ATC code L02BA03), of aromatase inhibitors (ATC code L02BG) and the presence of metastasis (in patients with data available data among the database; for details Supplementary Table S2). Hazard Ratio (HR) and 95% Confidence Interval (CI) were evaluated to predict total costs. A gamma distribution and identity link function (in order to retrieve non transformed costs) were applied; therefore, the coefficients are not reported on the logarithmic scale and are expressed in euros. Post estimation tests included residuals analysis and check for influential observations. No influential observations were identified, and residuals were normally distributed.

All analyses were performed using Stata SE version 17.0 (StataCorp, College Station, TX, U.S.A.).

3. Results

Among the study population, 3,647 aBC patients were included: 2,627 treated with palbociclib, 729 with ribociclib and 291 with abemaciclib. The mean age at inclusion (treatment start) was 63.5 ± 11.5 years in palbociclib-treated group, 62.0 ± 11.8 years in ribociclib-treated group, and 62.1 ± 12.2 years in abemaciclib-treated group (Table 1). The percentage of patients in pre-menopausal status ranged from 22.4% to 23.5% (Table 1). The evaluation of healthcare resource consumption was carried out in alive patient with at least one-year treatment: 1,009 treated with palbociclib, 249 treated with ribociclib and 38

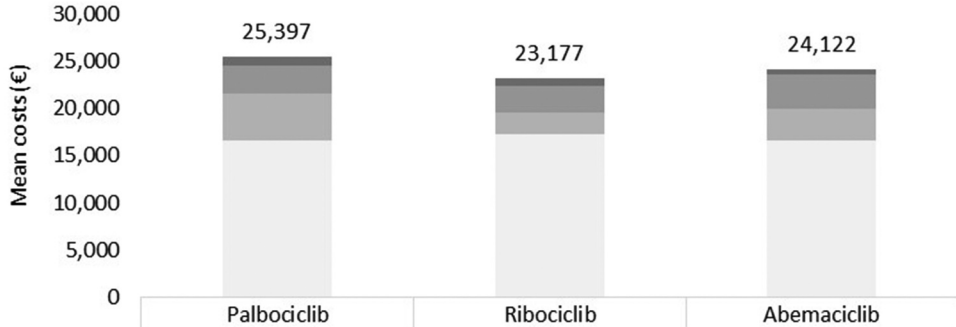
Table 1. Baseline characteristics of HR+/HER2-Abc patients included in the analysis (period: January 2017–June 2021) identified by at least one prescription for CDK 4/6i, divided by palbociclib, ribociclib and abemaciclib-treatment cohort.

	Palbociclib (*N* = 2,627)	Ribociclib (*N* = 729)	Abemaciclib (*N* = 291)
Age, years (mean ± SD)	63.5 ± 11.5	62.0 ± 11.8	62.1 ± 12.2
≤70 years (n, %)	1,738 (66.2)	517 (70.9)	201 (69.1)
>70 years (n, %)	889 (33.8)	212 (29.1)	90 (30.9)
Median (min-max)	64 (26–93)	63 (33–89)	63 (26–87)
Pre-menopausal status (n, %)	588 (22.4)	171 (23.5)	68 (23.4)
Post-menopausal status (n, %)	2,039 (77.8)	558 (76.5)	223 (76.6)

Table 2. Healthcare annual resource consumptions per patient during the first year of follow-up.

	Palbociclib (*N* = 1,009)	Ribociclib (*N* = 249)	Abemaciclib (*N* = 38)
CDK 4/6i prescriptions, mean ± SD	11.3 ± 2.0	10.7 ± 2.3	12.3 ± 2.6
Other drugs prescriptions, mean ± SD	9.3 ± 5.1	9.2 ± 6.0	7.9 ± 4.8
Visits prescriptions, mean ± SD	8.2 ± 7.6	7.6 ± 7.3	9.8 ± 6.8
Tests prescriptions, mean ± SD	15.2 ± 9.9	14.9 ± 9.1	18.5 ± 8.8
Hospitalizations, mean ± SD	0.2 ± 0.7	0.2 ± 0.7	0.1 ± 0.4

with abemaciclib were included in the analysis. Table 2 details the healthcare resource consumptions, calculated as number of CDK 4/6i prescriptions, other drugs prescriptions, specialist visits, diagnostic tests, and hospitalizations per patient in palbociclib, ribociclib and abemaciclib groups during the first year of treatment. The number of CDK 4/6i prescriptions per patient averaged 11.3 (in palbociclib), 10.7 (in ribociclib) and 12.3 (in abemaciclib) cohorts; for endocrine therapies it ranged between 7.9 and 9.3. The total annual direct costs related to resource consumptions during the first-year treatment averaged 25,397€ for palbociclib, 23177€ for ribociclib and 24,122€ for abemaciclib-treated patients, of which 4,851€, 2,265€ and 3,338€ for palbociclib, ribociclib and abemaciclib-treated patients, respectively, were related to other drugs (Figure 1). Tests were among the major driver of cost (CDK inhibitors excluded), accounting for 2,844€ for palbociclib, 2,623€ for ribociclib and 3,430€ for abemaciclib, while all-cause hospitalization costed a mean/patient of 837€ (palbociclib), 791€ (ribociclib) and 552€ (abemaciclib).



	Palbociclib	Ribociclib	Abemaciclib
Hospitalizations (€)	837	791	552
Tests (€)	2,844	2,623	3,430
Visits (€)	220	223	166
Other drugs (€)	4,851	2,265	3,338
CDK 4/6i (€)	16,645	17,275	16,636
Total (€)	25,397	23,177	24,122

Costs (median, min-max)	Palbociclib	Ribociclib	Abemaciclib
Hospitalizations (€)	0 (0-13,428)	0 (0 11,949)	0 (0 -7,113)
Tests (€)	1,926 (0-15,036)	1,634 (6 16,415)	3,416 (122 -9,781)
Visits (€)	124 (0-2,797)	121 (0-2,389)	128 (0-747)
Other drugs (€)	550 (0-9,746)	499 (0-9,227)	558 (0-2,672)
CDK 4/6i (€)	27,061 (805 -39,747)	23,327 (9,037 -34,774)	17,460 (821-27,438)

Figure 1. Healthcare direct costs during the first year of follow-up.

To identify predictors (among different baseline characteristics of patients) of total cost, a GLM analysis was carried out. As shown in Supplementary Table S3, treatment with abemaciclib and ribociclib was not associated with a significant impact on total cost compared to palbociclib (considered as a reference due to the larger sample size of the cohort). Moreover, age was associated with a cost decrease (−70.7€ for each year, $p = 0.004$), hormonal therapy was associated with a cost increase (+3,039€ with fulvestrant, $p < 0.001$) or decrease (−2,498€ with aromatase inhibitors, $p < 0.001$). The presence of metastases (especially bone, liver and brain lesions, evaluated in patients with data available within the database) was associated with cost increase (Supplementary Table S3).

The analysis of drug usage among included patients was evaluated up to 12 months of treatment period, with 3-month time intervals. In palbociclib-treated patients the daily mean dosage prescribed ranged from 117.64 mg/daily at 3 months to 102.01 mg/daily up to 12 months; for ribociclib-treated patients the daily mean dosage ranged from 568.66 mg/daily at 3 months to 475.31 mg/daily up to 12 months and for abemaciclib-treated patients the daily mean dosage ranged from 281.32 mg/daily at 3 months to 229.16 mg/daily up to 12 months (Supplementary Table S4). During the same treatment period, the mean number of drug packages dispensed was estimated; between 3 and 12 months it ranged from 3.29 to 11.56 for palbociclib-treated patients, from 3.23 to 10.94 for ribociclib-treated patients and from 6.77 to 22.66 for abemaciclib-treated patients (Table 3). The estimation of mean number of drug packages dispensed stratified by drug dosage are reported in Supplementary Table S5. During 12 months of treatment, among palbociclib-treated patients, 35% had a dose reduction with a mean of 8.9 wasted pills per patient; among those treated with ribociclib 22.1% had a dose reduction and no wastage of pills was found, as expected. In abemaciclib-treated patients, 44.7% had a dose reduction and a mean number of 6.7 wasted pills per patient (Table 4). At 12 months of treatment, the months to first reduction averaged 7.5 months (palbociclib), 7.6 months (ribociclib) and 6.6 months (abemaciclib); the mean time to second dose reduction was 11.3, 13.2, and 13 months in palbociclib-, ribociclib-, and abemaciclib-treated patients, respectively (not shown in the tables).

The estimation of total costs of therapy during the first year of treatment is reported in Table 5. The overall annual cost of therapy included patients' management with palbociclib was 21.24 million €, 5.34 million € for ribociclib and 0.52 million € for patients treated with abemaciclib. The projection of these data to the entire Italian population estimated 94.94 million € for palbociclib treatment, 23.86 million € for ribociclib and 2.31 million € for abemaciclib. The total cost of wasted therapy was 354,400€ (1.58 million € by Italian projection) for palbociclib-treated patients and 10,200€ in patients prescribed with abemaciclib (45,500€ by Italian projection) corresponding to the price updated to November 2021 of 528,716€ and 5,738€ per patient respectively with palbociclib (524€/patient) and abemaciclib (151€/patient). For ribociclib-treated patients, no wastage costs were estimated (Table 5) since the residual tablets could be administered in subsequent cycles after dose modification.

4. Discussion

This is a real-world analysis on drug usage and the economic impact of dose reduction in terms of drug wastage in HR+ HER2- aBC patients treated with CDK 4/6i in Italy.

Table 4. Number and percentages of patients with dose reduction and number of wastage pills during the first year of treatment period with palbociclib **(A)**, ribociclib **(B)**, and abemaciclib **(C).**

Treatment period	N. of patients	Patients with reduction	Wastage, pills
A. Palbociclib			
• up to 3 months	2,154	409 (19.0%)	7.9
• up to 6 months	1,638	464 (28.3%)	7.6
• up to 9 months	1,308	421 (26.4%)	8.8
• up to 12 months	1,009	353 (35.0%)	8.9
B. Ribociclib			
• up to 3 months	565	38 (6.7%)	/
• up to 6 months	431	64 (14.8%)	/
• up to 9 months	347	64 (15.3%)	/
• up to 12 months	249	55 (22.1%)	/
C. Abemaciclib			
• up to 3 months	189	36 (19.0%)	31.7
• up to 6 months	113	36 (31.9%)	24.0
• up to 9 months	81	32 (34.6%)	20.7
• up to 12 months	38	17 (44.7%)	6.7

Table 3. Mean number of drug packages dispensed during treatment period with palbociclib **(A)**, ribociclib **(B)**, and abemaciclib **(C)**. For each time point, the number of pre-menopausal, post-menopausal and overall women (in the mentioned order) for the three treatment cohorts is provided in brackets.

Treatment period	Pre-menopausal	Post-menopausal	Overall
A. Palbociclib			
• up to 3 months ($N = 496$; 1,658; 2,154)	3.30	3.28	3.29
• up to 6 months ($N = 369$; 1,269; 1,638)	6.01	5.92	5.94
• up to 9 months ($N = 302$; 1,006; 1,308)	8.72	8.64	8.66
• up to 12 months ($N = 249$; 760; 1,009)	11.67	11.52	11.56
B. Ribociclib			
• up to 3 months ($N = 134$; 431; 565)	3.33	3.19	3.23
• up to 6 months ($N = 95$; 336; 431)	6.18	5.72	5.82
• up to 9 months ($N = 71$; 276; 347)	8.63	8.18	8.27
• up to 12 months ($N = 47$; 202; 249)	11.26	10.87	10.94
C. Abemaciclib			
• up to 3 months ($N = 43$; 146; 189)	7.33	6.60	6.77
• up to 6 months ($N = 26$; 87; 113)	13.08	11.89	12.16
• up to 9 months ($N = 14$; 67; 81)	18.86	17.64	17.85
• up to 12 months ($N = 8$; 30; 38)	24.00	22.30	22.66

Table 5. Overall costs of therapy during first year of treatment and projection to Italian population.

	Palbociclib ($N = 1,009$)	Ribociclib ($N = 249$)	Abemaciclib ($N = 38$)
Total annual cost of therapy (€)	21,240,000	5,340,000	520,000
Total annual cost of therapy (€) (price updated to Nov-2021)	*16,794,805*	*4,301,475*	*632,168*
Total annual cost of wastage therapy (€)	354,400	0	10,200
Total annual cost of wastage therapy (€) (price updated to Nov-2021) [mean annual costs of wastage/patient]	*528,716 [524]*	*0*	*5,738 [151]*
Total annual cost of therapy (€) – Italian projection	94,940,000	23,860,000	2,310,000
Total annual cost of therapy (€) – Italian projection (price updated to Nov-2021)	*75,072,778*	*19.227,593*	*2,825,791*
Total annual cost of wastage therapy (€) – Italian projection	1,580,000	0	45,500
Total annual cost of wastage therapy (€) – Italian projection (price updated to Nov-2021)	*2,363,361*	*0*	*25,649*

Between January 2017 and June 2021, 3,647 aBC patients treated with CDK 4/6i therapy were included. The mean age at the start of treatment was 62 years and the majority of patients were in post-menopausal status (more than 75%). These data mirror those from a previous study conducted in aBC patients under CDK 4/6i, showing mean age at inclusion being 60 years old and 79–92% patients in post-menopausal status [24].

The number of drug packages dispensed over a 12-month treatment period was on average 11.6 for palbociclib, 10.9 for ribociclib and 22.7 for abemaciclib. The daily mean dosage tended to decrease over the first year of treatment for all medications, with 35% of palbociclib-treated, 22% of ribociclib-treated and 45% of abemaciclib-treated who experienced at least one dose reduction. These trends are consistent with previous reports available for the less recent drug palbociclib: in a retrospective analysis among US population 31% of patients with ≥6 months follow-up had experienced palbociclib dose reductions [25]. A series of RTCs conducted in US between 2009 and 2014 investigated palbociclib plus letrozole as first-line treatment of HR+ HER2- aBC patients (phase 2 studies PALOMA-1/TRIO-18 and PALOMA-2) [16,26] and the combination of the palbociclib and fulvestrant in HR+ HER2- metastatic cancer progressed on previous endocrine therapy (PALOMA-3) [27]. In all these trials, the patients in the palbociclib-treatment arm had at least one dose reduction, on average 40% in PALOMA-1, 36% in PALOMA-2 and 34% in PALOMA-3 [16,26,27].

The analysis of direct healthcare costs during the first year of treatment showed that, as expected, overall mean annual costs were mainly driven by CDK 4/6i; the total costs excluding these drugs ranged between 5,902 and 8,752€. Our findings are in general consistent with a previous work by Piccinni et al [28] reporting an average cost for managing patients with HR+/HER2- metastatic breast cancer of 7,543€ in the first follow-up year, in front of some differences, as the data by Piccinni refer to year 2013 when CDK 4/6i were not available yet and

could not be computed among the medication costs. The overall healthcare cost for the management of palbociclib-, ribociclib- and abemaciclib-treated patients were comparable between each other and the treatment itself did not predict the amount of total expenditures. Dose reductions led to drug wastage in patients treated with palbociclib and abemaciclib, but not in those on ribociclib, as it is only available in 200 mg tablets across all strengths, allowing dose adjustment without the necessity for a new prescription [16]. Consistently, the estimation of the total cost related to wastage therapy averaged 354,400€ for palbociclib and 10,200€ for abemaciclib-treated patients, while no drug wastage expenditure was observed for patients treated with ribociclib.

Previous analyses conducted in US and Chinese populations to compare drug wastage among palbociclib- and ribociclib-treated patients reported that drug wastage costs were higher in palbociclib than ribociclib regimen due to different dosing patterns [29,30]. In fact, while for palbociclib dose reductions may result in drug wastage due to the need to discard capsule to step down to a lower dose, the decrease of dosage in ribociclib-treated patients can simply be achieved by modifying the number of tablets consumed, potentially reducing drug wastage to zero [29,30].

These results must be interpreted considering the limitations related to the observational nature of the study, which was based on data collected from administrative databases. Our cohort of patients reflected real clinical practice by evaluating data from a subset of health-assisted individuals. The assessment of drug usage and drug wastage is based on prescriptions only and it is not possible to get insights into what patients do with unused pills; moreover, daily mean dosage could be influenced by the refill of the prescription: indeed, if a patient take a prescription before ending the previous one, the daily mean dosage could be slightly higher. This effect could be more evident in the limited time horizon (for instance the first trimester of treatment). Moreover, the estimation of the total cost of drug wastage is directly dependent on the number of patients treated with a certain medication. The GLM model to determine cost predictors took into account only variables collected; thus the impact of other variables was not considered.

5. Conclusions

In the area of oncology, the impact of pharmaceutical expenses and the potential drug wastage associated with dose adjustments represents an important component of economic evaluations on drugs. This real-world analysis investigated drug usage and related economic burden of CDK 4/6i therapy in aBC patients in Italy. Among the different subgroups of patients, comparable direct healthcare costs were observed. The evaluation of drug consumption showed that in palbociclib and abemaciclib-treated patients dose reduction led to drug wastage, with related expenses, while this phenomenon was not evident for ribociclib-treated patients. These results may support prescribers and healthcare policy decision-makers in highlighting drug wastage phenomenon to design a strategy to minimize this issue.

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Declaration of interest

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Author contributions

Study conception: S Palladino, E Premoli, D Valsecchi, M Suter, V Perrone, L Degli Esposti. Acquisition/analysis/interpretation of data: V Perrone, E Giacomini, D Sangiorgi, L Degli Esposti. Final approval of the publication: all authors.

Data sharing statement

All data used for the current study are available upon reasonable request next to CliCon s.r.l. which is the body entitled of data treatment and analysis by Local Health Units.

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