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Case Report

Clinical Prognosticators in Patients Treated with CDK 4/6 Inhibitors for Hormone Receptors Positive Advanced Breast Cancer

Isca Chrystel[1], Omarini Claudia[2], Cortesi Giulia[1], Moscetti Luca[2], Barbolini Monica[1], Dominici Massimo[1], Piacentini Federico[1]

[1]*Department of Medical and Surgical Sciences for Children & Adults, University Hospital of Modena, 41121 Modena MO, Italy;*
[2]*Division of Medical Oncology, University Hospital of Modena, 41121 Modena MO, Italy*

ABSTRACT

Background: CDK4/6 inhibitors are the new standard of care in hormonal receptors positive (HR+) advanced breast cancer (ABC). Phase III trials demonstrated an improvement in survival outcomes in patients with combined endocrine approach compared to endocrine therapy (ET) alone. The aim of this retrospective study was to assess prognostic factors for clinical response to CDK4/6 inhibitors.

Methods: All patients receiving CDK4/6 inhibitors from September 2016 to July 2019 were registered in a database. Data on tumor and patient's characteristics as well as concomitant medications were collected. Survival data were analyzed by Kaplan Meier curves and log rank test. Treatment toxicities were graded according to CTCAE v5. A drug-drug interactions analysis among CDK 4/6 inhibitors and co-administered medications was performed too.

Results: 121 patients were included in the study: 49% of patients treated in 1st -line, 25% in 2nd -line and 26% in 3rd –or further lines. 1st-line objective response rate (ORR) and clinical benefit rate (CBR) was 56% and 68%, compared to 40% and 50% in 2nd-line and 31% and 47% in heavily pre-treated patients, respectively. Median PFS according to line setting was: not reached in 1st-line, 17 months (95% CI 13-21) in 2nd-line and 7 months (95% CI 4-12) in 3rd or further lines. Negative prognostic factors in term of PFS were: previous chemotherapy for metastatic disease (p=0.0001), visceral metastatic sites (p=0.002) and endocrine sensitivity (p=0.001). No association among concomitant drugs administered and survival outcome was found. 94% of patients experienced neutropenia (G3-G4 60%) with 3% of febrile neutropenia. 71% of patients treated with Abemaciclib had diarrhea. Management of AE included 63% of treatment delay, 44% of 1st dose reduction and 15% of 2nd dose reduction, all due to neutropenia. No treatment discontinuation due to any toxicity was observed.

Conclusion: Data on efficacy and safety profile of CDK 4/6 inhibitors administered outside the context of a clinical trial are consistent with those reported in Phase III trials. Previous chemotherapy for metastatic disease, visceral metastatic site as well as previous endocrine sensitivity negatively affect CDK 4/6 inhibitors efficacy. Concomitant medications did not affect survival outcome or safety profile.

Keywords: CDK4/6 inhibitors; Metastatic breast cancer; Palbociclib; Ribociclib; Abemaciclib; Safety prolife

INTRODUCTION

In recent years, CDK 4/6 inhibitors have become the standard of care in hormonal receptor positive HER2 negative (HR+/HER2-) Advanced Breast Cancer (ABC) on the basis of survival benefits from Paloma, Monaleesa and Monarch Phase III Trials [1-6]. CDK 4/6 inhibitors plus Endocrine Therapy (ET) compared to ET alone double up survival outcomes in first line setting as well as after aromatase inhibitors failure [7,8]. Due to these impressive results, the majority of patients with HR+/HER2- disease are candidate to CDK 4/6 inhibitors as part of their treatment.

In this study, we retrospectively collected clinical-pathological and prognostic data on HR+/HER2- BC patients treated with CDK4/6 inhibitors at the University Hospital of Modena in order to identify significant prognostic factors.

PATIENTS AND METHODS

Patient population and treatment

Electronic medical records of all patients treated with CDK4/6 inhibitors for ABC in Modena Cancer Center from September

Correspondence to: Chrystel I, Division of Medical Oncology, University Hospital of Modena, 41121 Modena MO, Italy, Tel: +00390594222845; Email: claudia.omarini@gmail.com

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2016 to July 2019 were retrospective reviewed and collected.

All patients with a histologically proven diagnosis of HR+/HER2- BC treated with CDK 4/6 inhibitors plus endocrine-therapy based on standard guidelines were included. HR+/HER2- BC was defined as estrogen and/or progesterone receptors expression >1% and HER2 negative (score 0 or 1+ or ISH negative). Palbociclib, Ribociclib or Abemaciclib were administered according to Italian prescription status. Type of CDK 4/6 inhibitor, dose reductions/delays or drug discontinuation were applied and recorded as for clinician's judgement. Medical records were retrieved for demographic, clinical and molecular features of the disease, previous treatments and related outcomes, number and site of metastases at the time of CDK 4/6 inhibitor starting, objective response, date of disease progression and date of last follow-up or death. According to the duration of previous endocrine response, each patient was classified as endocrine sensitive (if relapsed at least 12 months after the completion of adjuvant endocrine therapy or with de novo ABC), primary resistant (if relapsed within 24 months while on adjuvant endocrine therapy or progressing within 6 months while on first-line endocrine therapy for advanced disease) or secondary resistant (if relapsed after 24 months of adjuvant endocrine therapy or within 12 months after ending adjuvant endocrine therapy or with a progression disease after at least 6 months of endocrine therapy for advanced disease) [15].

Concomitant medications, known to be potentially agonist or antagonist of CDK 4/6 inhibitors, were collected too. Considering their pharmacodynamics and pharmacokinetics, concomitant drugs were classified as CYP3A4 inducers or CYP3A4 inhibitors or CYP3A4 major substrates or Membrane transporter substrates [13,14]. A list of concomitant medications is available in supplementary material Table1 bis.

Table 1: Baseline characteristics for all patients included for analysis.

	Patients n°121 (%)
Median age	52 yrs (25-88)
Histology	
Ductal	85 (70)
Lobular	27 (22)
Other	9 (7)
Nuclear Grade	
1-2	46 (38)
3	28 (23)
Unknown	47 (39)
Ki67%	x
≤20%	78 (64)
>20%	30 (25)
Unknown	13 (11)
Stage at diagnosis	
Early Breast Cancer	87 (72)
Metastatic Breast Cancer	34 (28)
Metastatic sites	
Visceral	61 (51)
Non visceral	60 (49)
Number of metastatic sites	
1	44 (36)
2	45 (37)
≥3	32 (26)
Endocrine sensitivity	
Endocrine sensitive	48 (40)
Primary resistance	16 (13)
Secondary resistance	57 (47)
No concomitant medications	32 (26)
Concomitant medications	89 (74)
Cyp 3A4 Inducers	7 (8)
Cyp 3A4 Inhibitors	9 (10)
Major Cyp 3A4 substrates	66 (74)
Membrane transporter substrates	7 (8)
Neoadjuvant/adjuvant chemotherapy	63 (52)
Adjuvant Endocrine therapy	72 (59)
Tamoxifen	26 (36)
Aromatase inhibitors (Ais)	21 (29)
Exemestane	11 (15)
Tamoxifen switch to Ais	14 (19)
Chemotherapy for MBC	31 (26)
Endocrine therapy for MBC **Previuos Exemestane plus Everolimus**	31 (26) 9(7)
Type of CDK4/6 inhibitors	
Palbociclib	100 (83)
Ribociclib	14 (11)
Abemaciclib	7 (6)
Combination strategy	
Aromatase inhibitors	53 (44)
Fulvestrant	68 (56)

Treatment efficacy was evaluated according to RECIST criteria by CT and bone scan or PET/CT scan every 3-6 months, as for standard practice. Objective Response Rate (ORR) (defined as the percentage of patients with complete or partial response) and Clinical Benefit Rate (CBR) (defined as the percentage of patients with complete or partial response or stable disease for at least 6 months) were assessed too.

Toxicity was graded according to Common Terminology Criteria for Adverse Events (CTCAE v5).

The study was approved by the local Ethic Committee and conducted in accordance with the Helsinki Declaration. All patients released a written informed consent.

Statistical analysis

Variables were assessed by Pearson Chi-Square test or Fisher Exact test. Their impact on survival was tested in Cox uni/multivariate models. The multivariate Cox hazard model was built using stepwise regression (forward selection). Enter and remove limit were p=0.10 and p=0.15. The following variables were considered: previous systemic treatment, sensitivity to ET, type and number of metastatic sites. Survival outcomes of interest were Progression Free Survival (PFS: defined as the time from the date of the diagnosis to the date of the first documented relapse) and Overall Survival (OS: defined as the time from diagnosis of BC to death/last follow up). Survival was addressed by the Kaplan–Meier method and log-rank test. Significance was defined at $p \leq 0.05$ level. The Cox proportional hazard model was used to estimate Hazard Ratios (HR).

RESULTS

Patients and treatment characteristics

Overall, 121 patients diagnosed with HR+/HER2- ABC and treated with CDK 4/6 inhibitors from September 2016 to July 2019 in Modena Cancer Center were detected. Main patients and tumors characteristics are summarized in Table 1. In brief, median age was 52 years (25-88 years). More than half of patients received previous neo-/adjuvant chemotherapy. Adjuvant endocrine therapy was suggested in 72 women (59%), 45% of them received an aromatase inhibitor. Forty-eight (40%) patients were classified as endocrine sensitives, 16 (13%) as primary resistants and 57 (47%) as secondary resistants. Eight-seven patients (72%) experienced a relapse, with a median disease-free interval of 9.5 years (from 4 months to 30 years), being the other 34 patients (28%) diagnosed with de novo ABC. At treatment starting, 51% of patients had visceral disease; in particular, 63% had two or more metastatic sites. Seventy-four per cent of patients received concomitant medications, mainly major CYP3A4 substrates that could potentially increase CDK 4/6 activity and/or toxicity (Table 1 bis). Eighty-three per cent of women received Palbociclib as CDK 4/6 inhibitor, followed by Ribociclib (11%) and Abemaciclib (6%); plus an aromatase inhibitor in 53 patients (44%) or fulvestrant in 68 (56%) cases (Table 1). Forty-nine per cent of patients was treated in 1st line, 25% in 2nd line and 26% in 3rd or further lines (Table 2). Previous treatment with everolimus plus exemestane was administered in 9 patients (7%).

Efficacy

Overall, the median duration of CDK 4/6 inhibitor treatment was 21 months (95% CI 18,1 to 23,9 months). At the time of analysis, 49 patients had progressed on CDK 4/6 inhibitors and 14 died for BC. Median OS was not reached with 77% of patients alive at 5 years from the diagnosis of metastatic disease. As expected, efficacy of CDK 4/6 inhibitors significantly decreased according to the number of previous lines of treatment for metastatic disease.

First-line setting -The ORR was 56% with 6 cases of complete response. A stable disease was recorded in 10% of these patients. Overall, the CBR was observed in 40 patients (68%). At the time of the analysis, median PFS was not yet reached, and 65% of patients were still on treatment at 24 months of follow up (Table 2).

Second-line setting - The ORR was 40%. A stable disease was recorded in 10 % of these patients. Overall, the CBR was reported in 15 patients (50%). Median PFS of 17 months (CI 13-21 months) was calculated (Table 2).

Third- or further lines – Overall, the ORR was 31%. A stable disease was recorded in 16% of these patients. The CBR was observed in 15 patients (47%). Median PFS of 7 months (95% CI 4-12 months) (Table 2). In particular, five heavily pretreated patients (more than 5 lines of treatment for metastatic disease) stayed on CDK4/6 inhibitors for at least one year.

Considering clinical-pathological and prognostic data collected, chemo pre-treated patients showed a significant reduction in PFS compared to chemo-naïve ones (p= 0.0001) (Figure 1A). Furthermore, endocrine sensitive patients had significant longer PFS compared to endocrine resistant ones (p=0.001) (Figure 1B). Site of metastasis influenced the treatment efficacy too. Patients without visceral disease had prolonged PFS compared to those with visceral metastasis (mPFS Not reached vs 9 months, p=0.002) (Figure 1C). Multivariate analysis confirmed these results (Table 3). No significant differences were observed in median PFS according to concomitant medications.

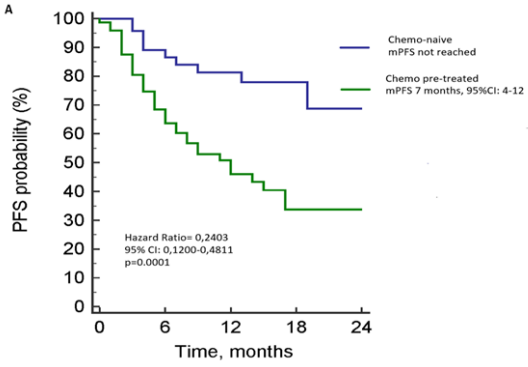

Figure 1a: Process of inclusion of Patients for the Study.

Table 2: PFS, ORR, CBR of CDK4/6 inhibitors.

	N° pts (%)	mPFS (months) (95% CI)	p value	ORR (%)	CBR (%)
Age classes					
< 35 years	5	17 (11-18)	0.981	80	100
36 -65 years	84	19 (17-24)		44	57
> 65 years	32	19 (12-19)		44	53
Nuclear grade					
1-2	46	19 (17-26)	0.223	52	63
3	28	13 (10-17)		36	61
Ki 67%					
≤ 20%	78	Not reached	0.135	47	63
>20%	30	18 (13-20)		40	47
Stage at the diagnosis					
Early breast cancer	87	17 (14-19)	0.722	44	59
Advanced breast cancer	34	Not reached		50	56

CDK 4/6 inhibitors treatment line					
1st	59	Not reached	0.0001	56	68
2nd	30	17 (13-21)		40	50
3rd or further lines	32	7 (7-14)		31	47
Previous adjuvant endocrine therapy					
Tamoxifen	26	13 (22-20)	0.675	46	54
Aromatase inhibitors	35	Not reached		33	52
Exemestane	11	12 (9-20)		45	64
Previous chemotherapy exposure					
Chemo-naïve	31	Not reached	0.0001	32	45
Chemo-pretreated	31	7 (4-12)		39	52
Endocrine sensitivity					
Endocrine sensitive	48	Not reached	0.001	60	73
Primary resistance	16	8 (2-11)		25	44
Secondary resistance	57	12 (7-17)		39	49
Number of metastatic sites					
1	44	Not reached	0.011	48	70
2	45	15 (13-20)		51	55
> 3	32	12 (9-20)		34	44
Site of metastasis					
Visceral disease	61	9 (6-19)	0.002	44	49
Non visceral disease	60	Not reached		47	67
Concomitant medications					
No concomitant drugs	32	15 (14-25)	0.913	44	53
Drugs that increase Cyp 3A4 activity	82	Not reached		45	61
Drugs that decrease Cyp 3A4 activity	7	Not reached		57	57

Abbreviations: N: Number; pts: Patients; mPFS: Median Progression Free Survival; CI: Confidence Interval; ORR: Objective Response Rate; CBR: Clinical Benefit Rate

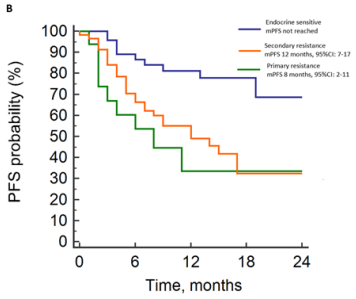

Figure 1b: Kaplan-Meier curves of PFS according to previous endocrine sensitivity. Abbreviations: mPFS: Median Progression Free Survival

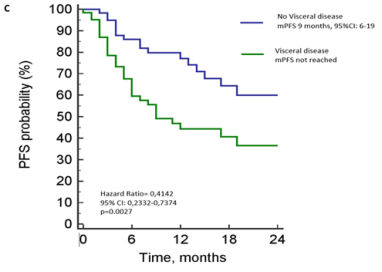

Figure 1c: Kaplan-Meier curves of PFS according to previous metastatic sites. Abbreviations: mPFS: Median Progression Free Survival

Table 3: Multivariate analysis of clinical-pathological factors for PFS.

	HR	95% CI	p
Previous chemotherapy (no vs yes)	1.93	1.53 - 3.53	0.032
Endocrine resistant (no vs yes)	2.67	1.31 - 5.41	0.006
Visceral disease (no vs yes)	2.06	1.12 – 3.78	0.019
N. of metastatic sites (1 vs > 2)	1.03	0.54 - 1.94	0.922

Abbreviations: HR: Hazard Ratio; IC: Confidence Interval; PFS: Progression Free Survival

Safety profile

In this patient population, data on toxicity confirmed CDK 4/6 inhibitors-related neutropenia as the most common adverse event (94% all grades and 60% Grade 3-4) with only 3% of cases of febrile neutropenia. All reported adverse events are listed in Table 4. The most common gastro-intestinal adverse event was diarrhea (12% of cases), in most cases in patients on Abemaciclib. Neither dose reduction nor discontinuation was applied due to diarrhea. All other toxicities were graded 1-2. Overall, no treatment discontinuation for AE was observed. Management of AE included treatment delay in 63% of cases, one-dose reduction in 44% and two-dose reductions in 15%. All the dose/treatment adjustments were due to neutropenia. No significant difference in AE was observed among subgroups of patients treated with concomitant

medications compared to patients with no concomitant drugs (Supplementary material Table 2).

Table 4: Adverse events.

Adverse events	All grades	Grade 3	Grade 4
	(%)	(%)	(%)
Haematological AE Neutropenia	94	54	6
Anemia	46	1	1
Thrombocytopenia	56	1	0
No Haematological AE Diarrhea	12	0	0
Nausea	9	0	0
Vomiting	6	0	0
Abdominal pain	8	0	0
Hypertransaminasemia	48	3	0
Xerosis	20	0	0
Arthralgia	11	0	0
Alopecia	9	0	0
Appetite loss	7	0	0
Pruritus	4	0	0
Fatigue	38	0	0

Abbreviations: AR: Adverse events

DISCUSSION

CDK 4/6 inhibitors approval has significantly changed the therapeutic algorithm of patients with HR+/HER2- ABC [1-6]. Paloma, Monaleesa and Monarch trials suggested that CDK4/6 inhibitors plus ET are more active than ET alone in all patients in both PFS and OS. An extended follow up analysis of Paloma 2 trial confirms the double up PFS advantage from the use of Palbociclib plus letrozole compared to ET alone in 1st line setting ($p<0.0001$) [16]. Similar data have been reported from Monaleesa 2 and Monarch 3 trials (Ribociclib plus ET median PFS 25.3 months vs 16 months; Abemaciclib plus ET median PFS 28.18 months vs 14.76 months, respectively) [3,4]. Statistically significant and clinically relevant advantages in OS were reported too [2,5,8]. The magnitude of benefit in OS showed in Monaleesa -3 and -7 and Monarch 2 studies was remarkable consistent: Ribociclib plus Fulvestrant median OS 40.2 vs 32.5 months, Ribociclib plus ET in premenopausal women OS rate 70.2% vs 46% at 42 months and Abemaciclib plus Fulvestrant median OS 46.7 months vs 37.3 months, respectively [2,5,8]. Recent data from real world experiences confirmed the efficacy and safety of CDK4/6 inhibitors even in un-selected population [9-11]. Results from our retrospective collection further support their efficacy. Considering first and second line, mPFS, ORR and CBR are consistent with those reported in registrative clinical trials [1-6]. Convincing benefit has been seen in heavily pretreated patients too, with a 47% of CBR and mPFS of 7 months. Evidence from two real world studies published on heavily pretreated population reporter a shorter mPFS compared to our data (4.5 months and 3.2 months, respectively). This discordance could be justify by the different definition of heavily pretreated patients, defined as patient treated in third or further line in our study population versus patients with at least four lines of systemic treatment in literature [19,20].

Despite the high rate of efficacy reported, clinical experience suggested that some patients benefit less from this class of drugs. The primary aim of our study was to clarify which clinical factors could be prognosticators for CDK 4/6 inhibitors. In particular, previous chemotherapy treatment for ABC, visceral disease and endocrine resistance were independent negative prognostic factors in term of PFS for women on CDK 4/6 inhibitors. In particular, chemo pre-treated patients had a mPFS of 7 months, compared to more than 50% of the chemo-naïve patients still on treatment at two years (Figure 1A). This finding can be explained by the fact that patient with HR+ disease treated with chemotherapy had more aggressive diseases from the beginning. Site of metastasis influenced the treatment efficacy too. Activity of CDK4/6 inhibitors was higher in patients without visceral involvement with a mPFS Not reached vs 9 months (Figure 1C, $p=0.002$). The predictive value of site of metastasis was concordant with those reported in the real world study by Pizzuti L. et al. Fifty-nine per cent of the patients without visceral disease was still on treatment at 1 year compared to 29.5% of those with visceral involvement, $p=0.001$ [12]. As expected, endocrine sensitive patients had significant better PFS compared to endocrine resistant ones (Figure 1B, $p=0.001$).

Regarding concomitant medications known to be inducers or inhibitors of CYP3A4, we performed an analysis in order to identify their possible interactions with CDK 4/6 inhibitors activity/toxicity. All CDK 4/6 inhibitors are major substrates for CYP3A4. In particular, they are inhibitors of CYP3A4 and the co-administration of them with strong or moderate CYP3A4 inhibitors may increase their AUC and, consequently, their risk of toxicity [13]. In our study, we classified concomitant medications as CYP3A4 inducers, CYP3A4 inhibitors, Major CYP3A4 substrates and Membrane transporter substrates. Based on our data, no significant differences were observed in term of toxicity or efficacy according to concomitant medications.

Data from clinical trials showed a favourable safety profile with quite manageable side effects [1-6]. Patient quality of life is maintained under therapy and, particularly in later line settings too [21-23]. The toxicity analysis confirmed a good tolerance to CDK 4/6 inhibitors without treatment discontinuation for AEs. Neutropenia was the most common haematological toxicity for palbociclib and ribociclib (95%-100% all grade with and 56%-71% of G3-4). As expected, Abemaciclib has a lower incidence of neutropenia with no G3-4 cases but a greater incidence of diarrhea compared to other CDK4/6 inhibitors (7%-9% Ribociclib/Palbiclib vs 71% with Abemaciclib). Despite that, no treatment discontinuation related to diarrhea was observed, probably due to the prompt intervention with antidiarrheal drug in case of symptoms.

Our study has some limitations. First, the small sample size and the length of follow up that was relatively short and overall insufficient to draw conclusions in terms of OS. The results of this analysis must be interpreted in light of multiple biases and weaknesses mainly, though not exclusively, stemming from its study design, i.e., retrospective, observational design. Despite that our analysis has relevant strengths, it provides evidence in support of the activity CDK 4/6 inhibitors in real-world practice, even in heavily pre-treated women.

CONCLUSIONS

CDK 4/6 inhibitors outside a context of clinical trial are safe, well tolerated, with a good efficacy, consistent with that reported in clinical trials. Previous chemotherapy for metastatic, visceral disease and endocrine resistant BC negatively affects CDK 4/6 inhibitors sensitivity. Co-administration of drug that is known to be substrates for CYP3A4 did not increase CDK4/6 inhibitors

toxicity or reduce efficacy.

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