Journal of Cancer Science & Therapy
ISSN: 1948-5956

Vazquez, et al. J Cancer Sci Ther 2019, 11:10

Review Article Open Access

Palbociclib Associated with Endocrine Therapy in Patients with Metastatic Breast Cancer: Predictive Factors of Severe Early Hematological Toxicity

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Abstract

Objectives: The addition of palbociclib to endocrine therapy has been shown to improve disease free survival in hormone receptor positive metastatic breast cancer patients. This cyclin CDK4/6 inhibitor exposes patients to a grade 3 or 4 hematological toxicity leading to discontinuation or an arrest of treatment that is associate with a dose-reduction intensity and potentially a lack of efficiency. The aim of this study was to identify predictive factors of severe early hematotoxicity (ESHT).

Methods: This retrospective observational cohort study included patients who started with palbociclib in the Institut Sainte Catherine between December 1, 2016 and January 1, 2019 for the treatment of metastatic breast cancer. Individual data and particularly hematological toxicity were collected from electronic medical records. Severe early hematotoxicity was defined as the occurrence, during the first 3 cycles, of grade 4 or grade 3 hematological toxicity requiring a dose-reduction of the drug.

Results: 181 patients (180 females) were included; median age was 67 years. 46 patients (25.4%) experienced an severe early hematotoxicity. Predictive factors of severe early hematotoxicity in multivariate analysis were a performance status (PS) of 2 or more (OR=3.77; 95% CI; p=0.024) and lack of radiotherapy of bone metastasis in the previous year (OR=0.30; 95% CI; p=0.003). Before palbociclib initiation, a neutrophil count below 3.37 G/L was predictive of severe early hematotoxicity with a sensibility of 76% and a specificity of 71%.

Conclusion: ECOG performance status, bone radiotherapy within the year and low baseline neutrophils count are associated with severe early hematotoxicity in palbociclib-treated metastatic breast cancer patients. These elements could be useful for a careful monitoring leading to adapted therapy.

Keywords: Palbociclib; Bone radiotherapy; Hematological toxicity; Metastatic breast cancer; Predictive factors; Retrospective study; Baseline neutrophils count

Introduction

Breast cancer is the most prevalent cancer and the first cause of cancer death worldwide in women [1]. In France, almost 60,000 new cases of breast cancer were diagnosed in 2017 and more than 10,000 died the same year [2]. Two-thirds of diagnosed breast cancers are hormone receptor positive (HR+) and, in metastatic disease, endocrine therapy showed efficacy in more than a half of the patients [3]. Hormonotherapy offers the best risk/benefit ratio in terms of cost and toxicity and endocrine therapy has been recognized as the gold standard for first-line treatment of HR+ metastatic breast cancer without visceral crisis [4]. However, new and acquired resistance to hormonal blockade is common and there are no guidelines for the choice of second line and subsequent therapy [5]. So, molecular targeted therapies as palbociclib, a D-cyclin dependent kinase 4/6-inhibitor of CDK4-retinoblastoma (Rb) pathway, have been introduced in order to prolong progression-free survival and, therefore, time for initiation of chemotherapy. Due to its antitumor synergistic activity, palbociclib associated with hormonotherapy became one of the major therapeutic options for first-line metastatic HER2 negative breast cancer without visceral crisis [3].

As expected for all drugs targeting the cell cycle, the main dose-limiting toxicity is bone marrow suppression as observed in clinical studies with palbociclib and mentioned in different reports focused on hematological toxicity [6,7]. Two thirds of patients experienced neutropenia, 35 to 50% are grade 3 or more [8,9]. Neutropenia grade 3 or 4 needs dose reductions and/or dose delay or temporary discontinuation leading to 6% of definitive arrest due to the neutropenia [10]. However, despite the elevated percentage of neutropenia episodes, febrile neutropenia occurred in only 1% of the cases [6].

Up to now, the only available data for evaluating risk-factors associated with hematological toxicity came from the clinical trials PALOMA-2 and PALOMA-3 [11,12]. Curiously, in these studies no classical factors, i.e., previous lines of chemotherapy, age, ECOG and the number of disease sites were significantly correlated to grade 3-4 hematological toxicity, except the racial status [11], particularly observed among the Japanese patients [12]. So, due to the lack of documented data, particularly in the post-authorization period, we conducted this retrospective analysis in patients receiving palbociclib to better define bio-clinical predictive markers of severe hematological toxicity.

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Received November 04, 2019; **Accepted** November 12, 2019; **Published** November 19, 2019

Citation: Vazquez L, Coussirou J, Arvers P, Rossi JF, Arnaud A, et al. (2019) Palbociclib Associated with Endocrine Therapy in Patients with Metastatic Breast Cancer: Predictive Factors of Severe Early Hematological Toxicity. J Cancer Sci Ther 11: 290-294.

Research Methodology

Patients and study design

Post-menopausal metastatic breast cancers treated with an association of endocrine therapy and palbociclib in first- or second-line hormonotherapy between December 1, 2016 and January 1, 2019 in the Institute Sainte-Catherine were identified via our pharmacy database. Data from both electronical and standard medical records were retrospectively analyzed. To be included in this study, patients need to have a histologically confirmed diagnosis of metastatic breast cancer and at least 3 complete cycles of palbociclib therapy or less than 3 cycles completion due to hematological toxicity. Each patient was followed up for at least four months after the first day of treatment for hematological toxicity. Data also included Eastern Cooperative Oncology Group (ECOG) index, age, weight, pretreatment blood cell count, cancer type, number of visceral and bone metastatic sites. Previous treatments were also collected, including history of adjuvant chemotherapy, metastatic chemotherapy, history of adjuvant and metastatic bone radiotherapy. In addition, start and end date of palbociclib treatment, line of therapy, starting dose, associated endocrine therapy were analyzed.

Endpoints

The main endpoint was to define the predictive factors for predictive factors of severe early hematotoxicity (ESHT). ESHT was defined as the occurrence hematological toxicity of grade 4 or of grade 3 requiring a dose reduction, including those following an initiation delay of next cycle until recovery to Grade ≤2 (10). Neutropenia represents the most common hematological side effect, appearing 15 days after the first dose of palbociclib mainly after the first or the second cycle and rarely after the subsequent cycles of therapy [11,13]. In this retrospective study, we defined an early toxicity when observed during the first three cycles of palbociclib. Hematological toxicity were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (version 4.3) [14]. As recommended, hematological lab tests were performed at day 1 and day 15 for the 2 first cycles and only at day 1 of all the following cycles [10].

Statistical analysis

Descriptive statistics are presented as mean (standard deviation) and median (range) for continuous variables. Discrete variables are reported as count (percentage). The Pearson $\chi 2$ test or the Fisher's exact test, when appropriate, were used to estimate the associations between categorical variables. The two-sided t-test or Wilcoxon rank sum test as appropriate were used for continuous variables. Significance was defined at the p value level below 0.05. Thereafter, a multivariate logistic model was built to analyze the primary end point based on selected parameters from the univariate analysis (the level of significance was set at p-value <0.20 for selection). A receiver operating characteristic curve (ROC curve) was performed to know the statistical significance threshold of continuous variables statistically significant on univariate analysis. Statistica (version 13.0) software was used for standard statistical evaluation and SPSS software for ROC curves.

Ethical considerations

No written informed consent was requested. First, we analyzed only previously and routinely collected information. Individual patient data were documented anonymously. Secondly, patients are informed that anonymized data can be analyzed and collected unless they are opposed. The local Ethics Committee approved this project.

Results

Patients

One hundred and eighty-one patients (180 women 1 man) were included in this retrospective analysis. Median age was 67 years [range 31-92 years old]. All the patients had ECOG index 0-3 with only 8.3% (n=15) known as presenting ECOG 2 or 3. There were 23 patients (12.7%) with non-specific ductal tumor type, 117 patients (64.6%) with ductal tumor type and 38 patients (21%) with lobular tumor type. Most patients (51.4%) received palbociclib plus fulvestrant, 42% palbociclib plus letrozole and 6.6% received palbociclib in combination with other antiestrogen therapies (anastrozole or exemestane). Initial dose of palbociclib was 125mg in 154 patients (85.1%), 100mg in 22 patients (12.2%) and 75mg in 5 patients (2.8%). At the time of data analysis, 70 patients (38.7%) were still receiving palbociclib.

Hematological toxicity

Forty-six (25.4%) patients presented ESHT as previously defined. Forty-five (97.8%) had neutropenia, including isolated neutropenia in 43 patients, neutropenia and thrombocytopenia in one patient and pancytopenia in one additional patient. Three patients (6.5%) had a thrombocytopenia, thrombocytopenia was isolated in one patient. Grade 4 hematological toxicity was observed in 17 patients (9.4%) including 16 patients having neutropenia and one patient having thrombocytopenia. Grade 3 hematological toxicity requiring dose reduction was observed in 35 patients with neutropenia (19.9%), including one patient with thrombocytopenia, 7 of them having previous grade 4. No febrile neutropenia occurred.

In univariate analysis (Table 1), the factors correlated with ESHT were ECOG index of 2 or 3 (17.4% vs. 5.2%), more than three bone metastases (84.8% vs. 59.3%), bone metastasis (93.5% vs. 78.5%), pelvis metastasis (73.9% vs. 46.7%), radiotherapy of bone metastasis (56.5% vs. 28.1%), bone radiotherapy within the year (37% vs. 18.5%), chemotherapy within the year (39.1% vs. 23%). Neutrophils baseline count was lower in patient with ESHT (2965/µL vs. 4102/µL) and patients with node metastasis experienced less hematotoxicity. As presented in Table 2, logistic regression analysis showed that predictive factors for hematological toxicity were an ECOG of 2 or more (OR=3.62, 95%CI 1.20-10.92, p=0.024) and the absence of radiotherapy of bone metastasis within the year was associated with less ESHT (OR=0.30, 95%CI 0.13-0.67, p=0.003). On the opposite, prior chemotherapy, number of lines of therapy and age were not associated with ESHT.

A ROC analysis was performed to calculate the threshold value that was predictive of hematological toxicity. The cut-off value of 3370 neutrophils/µL was determined with a specificity of 71.4% and a sensitivity of 75.8% (Area Under the Curve=0.785) (Figure 1). In addition, the predictive positive value was 47.4% and the predictive negative value was 89.7%.

Discussion

Management of patients with HR+ endocrine resistant metastatic breast cancer remains a challenge and the emergence of new targeted therapies such as palbociclib (and more recently abemaciclib and ribociclib) is a breakthrough for these patients. In this subgroup of patients as well as in patients without any systemic therapy for advanced disease, palbociclib has been proved to improve disease free survival [8,15–17]. CDK4/6 inhibitors are generally well tolerated, with only 2% of severe digestive adverse events and 2% of severe fatigue, as mentioned in 2 recent meta-analyses [9,18]. However, the most

Characteristic	Severe hematologic toxicity group n=46	No hematologic-toxicity group n=135	p-value§
Age, median (range) years old	69 (46-87)	65 (31-92)	0.18
Weight, Median (range), kg	63 (44-106)	65 (45-108)	0.58
ECOG performance status, n (%)			
0-1	29 (63)	95 (70.4)	**0.013**
2-3	8 (17.4)	7 (5.2)	
Unknown	9 (19.6)	33 (24.4)	
Cancer type, n (%)			***Ductal vs. other***
Ductal Non specific	3 (6.5)	20 (14.8)	0.38
Ductal	31 (67.4)	86 (63.7)	
Lobular	12 (26.1)	26 (19.3)	
Other	0	3 (2.2)	
Disease site, n (%)			
Visceral	25 (54.3)	90 (66.7)	0.13
Node	16 (34.8)	74 (54.8)	**0.019**
Bone	43 (93.5)	106 (78.5)	**0.024**
Number of bone metastases, n (%)			
≥ 3 < 3	39 (84.8) 7 (16.3)	80 (59.3) 55 (40.7)	**< 0.01**
Number of disease site (off-bone), n (%)			***<5 vs. ≥5***
0	15 (32.6)	33 (24.4)	0.17
1-4	17 (37)	47 (34.8)	
5-10	2 (4.3)	14 (10.4)	
>10	11 (23.9)	40 (29.6)	
Bone metastases sites, n (%)			
Spine	39 (84.8)	97 (71.9)	0.080
Pelvis	34 (73.9)	63 (46.7)	**<0.01**
Locoregional irradiation, n (%)			
Mammary gland	31 (67.4)	78 (57.8)	0.27
Chest wall	18 (39.1)	43 (31.9)	0.35
Node area	31 (67.4)	76 (56.3)	0.14
Prior metastatic radiotherapy, n (%)			
Bone radiotherapy Pelvis radiotherapy	26 (56.5) 13 (28.3)	38 (28.1) 18 (13.3)	**<0.01** **0.039**
Spine radiotherapy	17 (37)	24 (17.8)	**0.017**
Bone RT in the year	17 (37)	25 (18.5)	**0.011**
Adjuvant endocrine sensitivity, n (%)			
Resistant	10 (21.7)	46 (34.1)	0.082
Sensitive	22 (47.8)	48 (35.6)	
Not applicable*	14 (30.4)	41 (30.4)	
Metastatic endocrine sensitivity, n (%)			
Resistant	9 (19.6)	28 (20.7)	0.74
Sensitive	36 (78.3)	97 (71.9)	
Not applicable**	1 (2.2)	10 (7.4)	
Prior chemotherapy, n (%)			
Adjuvant	27 (58.7)	77 (57)	0.85
Metastatic	21 (45.7)	47 (34.8)	0.19
Chemotherapy in the year, n (%)	18 (39.1)	31 (23)	**0.033**
Initial dosage palbociclib, n (%			***125 mg vs. other***
125 mg	40 (87)	114 (84.4)	0.68
100 mg	4 (8.7)	18 (13.3)	
75 mg	2 (4.3)	3 (2.2)	
Hormonal therapy associated, n (%)			***Fulvestrant vs. other***
Fulvestrant	24 (52.2)	69 (51.1)	0.90
Letrozole	21 (45.6)	56 (41.5)	
Anastrozole	0	5 (3.7)	
Exemestane	1 (2.2)	5 (3.7)	
Treatment line			***1 vs. 2 vs. >2***
1	23 (50)	76 (56.3)	0.40
2	9 (19.6)	31 (23)	
3	4 (8.7)	12 (8.9)	
≥ 4	10 (21.7)	16 (11.9)	
Neutrophils count. Median (range). cells/µL	2965 (1091-5572)	4102 (600-11989)	**<0.01¤**
Platelet count. Median (range), G/L	232 (73-403)	259 (109-682)	0.065¤
Hemoglobin rate Median (range), g/dL	12.7 (9-14.9)	13.1 (9.5-16.2)	0.10¤

*Not applicable. metastatic from the beginning or without adjuvant endocrine therapy
¨Not applicable. endocrine therapy started for less than 6 months
§ The data were evaluated with χ^2 test or Fisher's test when appropriate.
¤ The data were evaluated with Wilcoxon rank sum test

Table 1: Patient baseline demographic, clinical and biological characteristics in the hematologic toxicity population and in the population without hematologic toxicity.

Variables	Final LR model		
	OR	95% CI	p-value
Absence of metastatic bone radiotherapy in the year *(Yes vs. No)*	0.30	0.13-0.67	0.003
Baseline ECOG *(0-1 vs. 2-3)*	3.62	1.20-10.92	0.024

LR: Logistic Regression; OR: Odds Ration; 95% CI: 95% Confidence Interval

Table 2: Multivariate analysis of factors associated with early severe hematotoxicity.

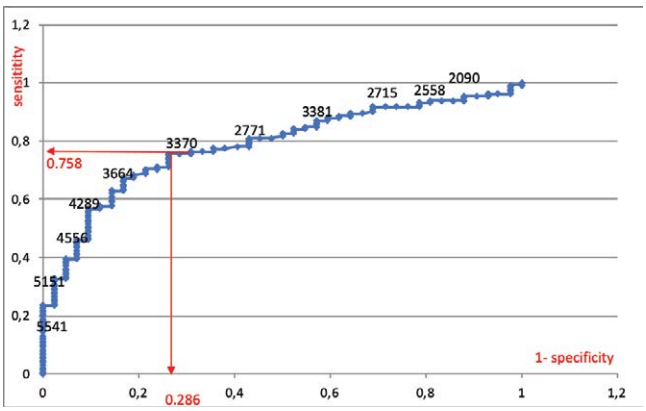

Figure 1: Receiver Operating Characteristic (ROC) analysis of neutrophils baseline count.

common toxicity remains hematological toxicity [9,18]. The frequency of ESHT we found in our study is lower than that observed in the literature (25.4% of ESHT). In prospective, randomized phase II and III trials, palbociclib combined with endocrine therapy resulted in a rate of grade 3-4 neutropenia, thrombopenia and anemia of respectively 54%

and 66%, 3% and 1.6%, 2.6% and 6% [8,15-17]. However, our results are consistent with studies including grade 4 or 3 side effects resulting in a palbociclib dosage reduction: respectively 29.8% and 27% in two studies of 845 (pooled data of PALOMA-1, -2, -3) and 411 metastatic breast cancer patients treated with palbociclib plus endocrine therapy [13,19]. As expected, the most common hematological toxicity observed in our cohort was neutropenia. In addition, we found that isolated neutropenia was the main hematological toxicity (93.5%), the same level that is observed in different Phase II/III studies and post-authorization (Phase IV) reports, representing the « real-life » of palbociclib usage [6,8,9,11,15–17,19]. Despite a high rate of early severe hematological toxicity, we did not find any febrile neutropenia, as observed in different studies associated with 1% of febrile neutropenia episodes [9,13].

In addition, rare studies have analyzed the diverse predictive factors for hematological toxicities in such patients. Consistent with the data published by Verma S et al., we also found that early severe hematotoxicity occurred independently of prior chemotherapy, age and number of diseases [11]. In this post hoc analysis of toxicity of patients included in the study PALOMA-3, Asian ethnicity and below-median neutrophil counts at baseline were significantly associated with an increased risk of developing grade 3–4 neutropenia with palbociclib [11]. In the same way, in the PALMOA-2 trial, the most common adverse events (AEs) were hematological AEs which were more frequently observed in the Japanese population than in the standard population (neutropenia: 93.8% [87.5% grade 3/4] vs. 79.5% [66.4%]; leukopenia: 62.5% [43.8%] vs. 39.0% [24.8%]) (12). As we did not include patients of Asian origin in our study, we are unable to analyze this previously observed predictive factor. We also found that a lower neutrophil cell count at the initiation of palbociclib therapy was correlated with high risk to develop ESTH (median 2965/µL vs; 4102/µL $p<0.01$). Subsequent ROC analysis showed that a value below 3370 neutrophils/µL before palbociclib initiation was predictive of a severe early hematotoxicity with a sensitivity of 75.8% and a specificity of 71.4%.

In our real-life study, an ECOG of 2 or more was identified as a risk factor of ESHT during palbociclib treatment (OR=3.62; 95CI% 1.20-10.92). Patient ECOG index was not associated with hematotoxicity in the post hoc analysis of PALOMA-3, as well as the majority of Phase III studies, but we must keep in mind that these studies only included patients with an ECOG index of 0 or 1 [11]. ECOG performance status plays a role both in prognosis assessment and to adapt therapy to patient's clinical conditions. Patients with bad ECOG index including limited functional capacity tend to have worse conditions to tolerate anti-cancer drugs [20].

Exposure to ionizing radiation directly damages hematopoietic stem cells and alters the capacity of bone marrow stromal elements to support and/or maintain hematopoiesis *in vivo* and *in vitro* [21]. Old clinical studies have demonstrated that the extent of radiation-induced bone marrow injury depends on both the radiation dose and the volume of BM irradiated but not on the irradiated area [22]. So, an increase even in low-dose to pelvic bony structures can significantly predict for white blood-cell-count decrease [23]. In addition, sparing just a portion of pelvic bone marrow seems insufficient to decrease rates of clinically significant bone marrow suppression as shown in a study of 45 patients with anal cancer receiving definitive chemoradiation, where doses to total pelvic bone marrow or to other anatomically defined pelvic subsites were individually associated with hematological toxicity [24]. That is probably the reason why in our study, bone metastasis radiotherapy within the year (OR=0.30; 95CI% 0.13-0.67), but not history of spine or pelvic metastasis radiotherapy was associated with severe early hematotoxicity.

Our study has several limitations, including the retrospective design and the absence of hematological toxicity chronology and nadir. We found ECOG index to be a predictive factor of ESHT but ECOG index has a poor inter-observer reproducibility and a low concordance rate between the evaluations carried out by physicians and by patients [25]. We did not consider the baseline lymphocytes count that has been shown to be predictive of hematological toxicity in patients treated with chemotherapy [26]. Finally, we did not include all concomitant treatment in the analysis. Nevertheless, it is a real-life study with a relatively large number of patients that has identified reliable hematotoxicity predictive factors.

Conclusion

In conclusion, this study found that ECOG index, radiotherapy of bone metastasis in the year and neutrophils count before treatment initiation could predict palbociclib severe early hematological toxicity in patients with metastatic HR+ breast cancer. As the therapeutic window of any new treatment regimen needs to be evaluated for efficacy vs. the clinically tolerable safety profile, particularly in the advanced disease setting, these daily clinical practice clinical and biological parameters could be easily used for screening a population that could be managed by closer monitoring or early dose reduction to maintain a maximum dose-intensity and an increase quality of life. Other studies are needed to confirm our results in breast cancer patients and also in other tumor types.

Acknowledgements

The Unit for clinical research in the Institut Sainte-Catherine acknowledged for their support.

Author Contributions

JC and PD conceived of and designed the study. JC, CS and LV identified eligible patients. LV and CS collected the data. LV and PA analyzed the data. LV drafted the manuscript. PD, JC, AA, JG and JFR critically revised the manuscript for important intellectual content. All authors read and approved the final manuscript version.

Availability of Data and Materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Ethical Approval and Consent to Participate

No written informed consent was requested. First, we analyzed only previously and routinely collected informations. Individual patient data were documented anonymously. Secondly, patients are informed that anonymized data can be analyzed and collected unless they are opposed. The local Ethics Committee approved this project.

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