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Taxane rechallenge during metastatic disease in HER-2 negative breast cancer patients: Clinical activity, tolerance and survival results

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ABSTRACT

Background: Taxanes are major drugs for metastatic breast cancer (MBC) treatment, and are generally well tolerated, making them attractive for therapeutic reintroduction (rechallenge) during metastatic course. In view of the paucity of current literature, we questioned the usefulness of taxane rechallenge in a population of patients previously treated with taxanes in a metastatic setting.

Methods: From the local database of a French cancer center, we retrospectively identified 756 patients diagnosed with ER+/HER2-, or triple negative MBC, and treated between 2008 and 2021. Among them, 58 patients (7.8%) were rechallenged with taxanes. Clinical characteristics, response rates, and survival were retrospectively evaluated and compared to patients who received taxanes only once.

Results: Compared to non-rechallenged population, patients treated with taxane rechallenge were significantly younger, with better general status, and received more treatment. First taxane exposure led to better tumor response and was more frequently discontinued for reasons other than progression, compared to the non-rechallenged population. Taxane rechallenge led to an objective response rate of 27.6%, and a clinical benefit rate of 46.6%, with a median progression-free survival (PFS) of 5.7 months, and a median overall survival (OS) of 11.6 months. We also found a PFS2/PFS1 ratio >1.3 in 55.2% of the rechallenge population.

Conclusion: Although only a minority of MBC patients are concerned, taxane rechallenge appears to be a pragmatic option with an acceptable tolerance, and good efficacy, especially when these drugs have shown clinical activity earlier in the disease course, and/or have been stopped for reasons other than progression.

1. Introduction

Despite the great strides made in cancer treatment in recent decades, metastatic breast cancer (MBC) remains a major public health problem and an incurable disease. In 2022, chemotherapy remains a major option for MBC, with single-agent sequential treatment usually preferred over combination treatments, because of an increased toxicity risk and a lack of impact on overall survival [1]. Disease progression after a given treatment is classically considered as the reflection of the cancer cells' resistance to this treatment, and often leads to another line of treatment. However, when all the major drugs have already been used in the metastatic setting, the question of rechallenge with a previously administered drug may arise. Theoretically, rechallenge could make it possible to target a sensitive clonal population of tumor cells not recently exposed to the treatment. This approach is current clinical practice in metastatic colorectal cancer. In prostate cancer, taxane rechallenge with both docetaxel and cabazitaxel has shown interesting results in terms of PSA and radiological responses [2].

Metastatic breast cancer is usually considered a chemosensitive disease, with many available cytotoxic drugs having shown clinical efficacy, including in heavily pre-treated patients. This probably explains why rechallenge with a given chemotherapy is not currently part of the treatment recommendations [1,3]. However, it is not uncommon to encounter a patient with MBC who has received all of the recommended

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chemotherapy molecules, and who suffers disease progression, despite being in good general condition. In these circumstances, chemotherapy rechallenge with a well-tolerated drug, such as taxanes, may be an option.

Taxanes, together with anthracyclines, capecitabin, and eribulin, count among the major families of chemotherapy used in breast cancer, both at early stages and in the metastatic setting. In MBC, high response rates (25–70% as first-line treatment [4]) and good tolerance have been reported. Nonetheless, cumulative toxicity in the form of peripheral neuropathy can impact quality of life, and therapeutic discontinuation for this form of toxicity is common in routine care. Thus, a certain proportion of patients are likely to stop taxanes without having observed resistance to this treatment, and the resumption of taxanes could be discussed in case of progression or later.

In this study, we investigated taxane rechallenge in patients with MBC from a locally-based population in a French cancer center. We evaluated the clinical efficacy of taxane rechallenge through objective response rates and best response obtained, and exploratory progression-free survival (PFS) and overall survival (OS) analyses. Tolerance of taxane rechallenge was also examined.

2. Patients and methods

2.1. Patients

Data of patients with metastatic HR+/HER2-breast cancer (BC) and metastatic triple negative breast cancer (mTNBC) treated for metastatic disease between 2008 and 2021 were extracted from the local database of the Centre Georges-François Leclerc in Dijon (France). HER2+ MBC were excluded to avoid confounding bias, due to the concomitant use of anti-HER2 targeted therapies with taxanes. Patients' clinical characteristics, tumor characteristics, previous use of taxanes as adjuvant or neoadjuvant therapy, use of maintenance treatment after first taxane exposure, reason for taxane discontinuation, best response to taxane (complete response (CR), partial response (PR), stable disease (SD), or progressive disease (PD)) and toxicity were collected.

Patients treated with taxanes in association with another drug during first exposure were also included, but patients treated with a chemotherapy combination during taxane rechallenge were excluded to avoid bias.

For the purposes of comparison, we also collected the same data for local MBC patients treated with taxanes, but not rechallenged with this cytotoxic family.

2.2. Statistical analysis

The rechallenge population was compared with the local HER2- MBC population treated only once with taxanes (control population) using the Chi2, Fisher or Wilcoxon tests as appropriate.

CR, PR, SD and PD were defined according to the RECIST criteria based on routine radiological follow-up. First taxane exposure was defined as the duration between the day of the first administration of taxanes for MBC and the day of the last administration of taxanes in the same line of treatment. Second taxane exposure (rechallenge) was defined as the time between the first and last day of the second taxane adminstration for MBC. PFS for first taxane exposure was defined as the duration between the day of the first administration of taxanes for metastatic disease and beginning of the next line of treatment. Of note, if a maintenance treatment was given, the duration of the maintenance treatment was included in PFS. PFS for taxane rechallenge and PFS in-between lines were defined in a similar manner. Due to heterogeneity in chemotherapeutic lines of treatment, a PFS2/PFS1 ratio was estimated, in which each patient is their own control, where PFS2 is the PFS for taxane rechallenge, and PFS1 is the PFS for the prior line of treatment. Since PFS usually decreases over lines of treatment during the natural course of MBC, a PFS2/PFS1 ratio >1.3 was proposed to define a treatment benefit in non-homogeneous heavily pre-treated patients [5].

Sankey plots were built to describe the trajectories of patients according to their best tumor response obtained on the first, second and (if available) third exposure to taxanes. Survival curves and survival rates were determined using the Kaplan Meier method, and were compared with the log-rank test. The impact of clinical or tumor characteristics on PFS was determined by univariate Cox models. Logistic regression models were performed to identify the characteristics associated with a PFS2/PFS1 ratio >1.3.

All tests were 2-sided, and the significant threshold was 5%. Analyses were performed using SAS version 9.4 (SAS Institute Inc., Cary, NC, USA).

3. Results

3.1. Study population

The local database population was composed of 925 patients diagnosed with MBC and treated between 2008 and 2021 (Fig. 1). We excluded 169 patients with HER2+ MBC (19.5% of the population) and 8 patients with no HR and/or HER2 status available (0.9% of the population). In the remaining 748 patients, 625 (83.6%) presented with an HR+/HER2- MBC, and 123 patients (16.4%) presented with a metastatic TNBC. In this HER2-negative population, 68.4% of patients received taxane-based chemotherapy during their metastatic history (89.3% with paclitaxel and 10.7% with docetaxel), and 58 patients (7.8%) received at least one taxane rechallenge during metastatic disease.

3.2. Comparison of control and rechallenge populations

We compared the patients' characteristics between the control population and the rechallenge population (Table 1). Among the 454 patients of the control population, 4 were men, whereas in the rechallenge population all patients were females. Median age was 56.5 years old in the rechallenge population and 64 years old in control population, making patients from rechallenge population significantly younger ($p = 0.0005$). Rechallenged patients also had a better general condition at the time of diagnosis of metastatic disease ($p = 0.0072$), with all patients presenting with WHO status of 0 or 1. The median number of treatment lines was higher in the rechallenge population, with a median of 7 lines ($p = 0.0001$). The other clinical characteristics were comparable, with no statistically significant differences. Especially, taxanes were used in an early setting (adjuvant or neoadjuvant) in 33.7% of the control population and 29.3% of the rechallenge population.

3.3. Taxane treatments

We compared the characteristics of taxane treatment between the population of patients with HER2- MBC who were not rechallenged with taxanes (control population), and the rechallenged population (Supplementary Data 1). Taxanes were used as frontline chemotherapy for metastatic disease in 79.3% of the rechallenge population and in 70.9% of the control population. First taxane exposure in metastatic disease was with paclitaxel for a large majority of patients (72.4% in the rechallenge population and 91.4% in the control population). Taxanes were combined with another treatment in 74.1% of the rechallenge population and in 67% of the control population; the associated treatment was mainly bevacizumab in both populations, but could also be another cytotoxic chemotherapy. Details of taxane treatments in the rechallenge population are given in Supplementary Data 2A-B. Paclitaxel was preferred over docetaxel as the second taxane (rechallenge) and third taxane exposure, with respectively 91.4% and 75% in the rechallenge population. 38 patients (65.5%) from the rechallenge population received the same taxane molecule both the first and second time, and 20 (34.5%) received two different taxane (Supplementary Data 2A).

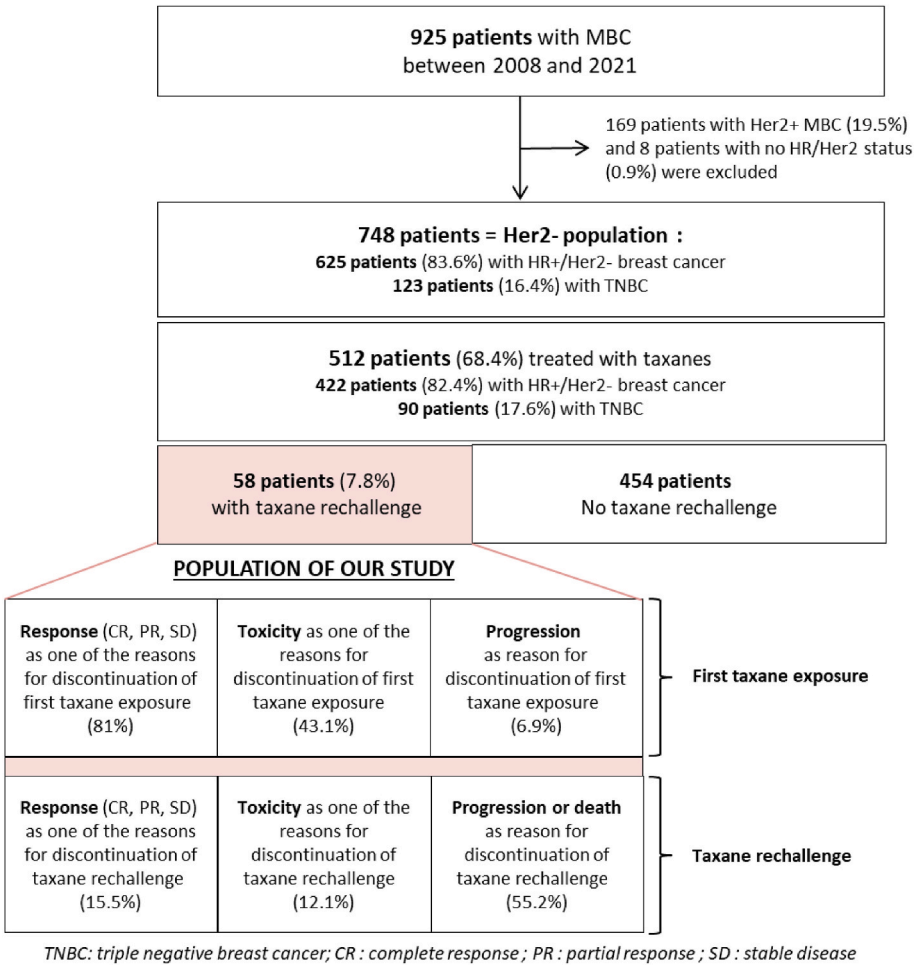

Fig. 1. Flow chart. Patients from the local MBC database (Centre Georges-François Leclerc, Dijon); in the study population (N = 58), repartition of favorable response, toxicity and disease progression as reasons for taxane discontinuation are indicated.

3.4. Other lines of treatment

Between first taxane exposure and taxane rechallenge, in the rechallenge population, the median number of treatment lines (either endocrine therapy or chemotherapy) was 2 (range [0–8]), with 0 corresponding to the rechallenge of taxane after a therapeutic break or maintenance therapy. Out of the 52 patients without disease progression and/or further line of treatment, seven (13.5%) were given a therapeutic break after first taxane exposures and forty-five patients (86.5%) were given maintenance therapy (Supplementary Data 2B). 42.2% received maintenance with endocrine therapy alone (19/45), 15.6% with chemotherapy alone (for instance capecitabine), and 42.2% with other combinations of maintenance treatment, such as capecitabine + endocrine therapy or bevacizumab. The median taxane-free interval between the two exposures was 23 months, and a large majority of patients (93.1%) experienced taxane rechallenge after an interval of at least 4 months. Of note, no significant difference was observed in terms of best therapeutic response between rechallenge after a short or a long taxane-free interval (greater than or less than 4 months).

3.5. Tolerance and reasons for taxane discontinuation

A tumor response that has been deemed sufficiently favorable (either CR, PR or SD) was one of the reasons for first taxane discontinuation in 81% of patients in the rechallenge population, but in only 48% of the control population ($p < 0.001$). Concerning first taxane exposure, toxicity was one of the reasons for treatment discontinuation in 43.1% of patients in the rechallenge population and in 30% of the control population ($p < 0.001$). The first taxane treatment was stopped following disease progression in only 6.9% of patients in the rechallenge population, compared to 46.9% in the control population ($p < 0.001$).

A sufficient favorable response (CR, PR, or SD) was also found as one of the reasons for taxane discontinuation after taxane rechallenge in 15.5% of the patients, toxicity in 12.1%, and progression (including palliative care decision or death) in 55.2%. Four patients (6.9% of the rechallenge population) were prescribed a second taxane rechallenge, using paclitaxel in 3 patients (75%) and docetaxel in 1 patient (25%). One patient (treated with paclitaxel) eventually stopped the treatment because of peripheral neuropathy and was prescribed hormone therapy for nearly 3 months; 2 patients stopped taxanes because of disease progression and 1 patient died.

We collected toxicity data in the rechallenge population (Supplementary Data 3): in these patients, the first exposure to taxanes resulted in peripheral neuropathy reported in 50% of cases (including 25.9% grade 3 neuropathy, contributing to taxane discontinuation). Other toxicities included paronychia (24.1%), mucous membrane disorders (31%), contributing to taxane discontinuation respectively in 10.3% and 6.9% of cases. In this same population, during taxane rechallenge (second taxane exposure), hematotoxicity was found in 24.1% of the patients, peripheral neuropathy in 48.3% (with only 3.4% of grade 3 contributing to taxane discontinuation), digestive disorders in 20.7% and asthenia and water retention were respectively found in 15% and 15.5% of the patients.

Table 1
Comparison of patient characteristics at metastatic disease diagnosis between patients with taxane rechallenge and the control population.

Variable	Rechallenge population (N = 58)	Control population (N = 454)	P value
Sex			1
Male	0	4	
Female	58	450	
Age at metastatic diagnosis, years			**0.0005**
Median [min - max]	56.5 [29.0–78.0]	64.0 [26.0–93.0]	
WHO status at metastatic diagnosis			**0.0072**
0	37 (63.8%)	192 (42.3%)	
1	21 (36.2%)	215 (47.4%)	
2	0 (0.0%)	37 (8.1%)	
3	0 (0.0%)	9 (2.0%)	
4	0 (0.0%)	1 (0.2%)	
Histological type at metastatic diagnosis			0.5416
Ductal carcinoma	50 (86.2%)	377 (83.0%)	
Lobular carcinoma	8 (13.8%)	76 (16.7%)	
Other	0	1 (0.2%)	
Immunohistochemical subtype			0.3534
HR+/HER2-	49 (84.5%)	360 (79.3%)	
TNBC	9 (15.5%)	94 (20.7%)	
Metastatic disease at diagnosis			0.659
De novo	15 (25.9%)	130 (28.6%)	
Metastatic relapse	43 (74.1%)	324 (71.4%)	
Metastatic sites at metastatic diagnosis			0.3727
Bone-only metastases	13 (22.4%)	80 (17.6%)	
Lymph-node metastases	4 (6.9%)	39 (8.6%)	
Visceral metastases	41 (70.7%)	335 (73.8%)	
Number of initial metastatic sites			0.0564
Median [min - max]	2.0 [1.0–6.0]	2.0 [1.0–7.0]	
Previous use of taxane in early setting			0.6027
Yes	17 (29.3%)	153 (33.7%)	
Lines of treatment (total[a])			**0.0001**
Median [min - max]	7.0 [2.0–14.0]	3.5 [1.0–12.0]	

NS, not significant; HR, hormone receptor; TNBC, triple negative breast cancer.
[a] Including endocrine treatment in HR + MBC.

3.6. Clinical efficacy: tumor response obtained with taxane treatments

We collected the best tumor response obtained with taxane treatments in both populations. Best response obtained during first exposure and rechallenge to taxanes are shown in Fig. 2 and in Sankey plots (Fig. 3). Regarding first taxane exposure, objective response rate (ORR) and clinical benefit rate (CBR) were significantly different between the control and rechallenge populations ($p < 0.001$) (Fig. 2). Of the 58 patients in the rechallenge population, 72.4% showed objective response to the first taxane (CR for 22.4% and PR for 50%), whereas in the control population, only 40.5% responded to first taxane exposure with CR or PR. Stable disease was recorded as the best response in 22.4% of the rechallenge population and 24.2% of the control population, and progressive disease in respectively 5.2% and 35.3%.

Regarding second taxane exposure (taxane rechallenge), 27.6% of the population showed either CR or PR as best therapeutic response, and nearly 2 out of 3 were prescribed maintenance therapy (a third with capecitabine and two thirds with endocrine therapy). 19% showed SD as their best therapeutic response. 2 patients (3.4%) still had paclitaxel ongoing at the study cut-off date.

Fig. 3 illustrates the best therapeutic response over time for each patient in the rechallenge population. Among the 13 patients with CR as best response to first taxane exposure in the metastatic setting (T1), 30.8% showed an objective response during second exposure (T2) and 23.1% had SD. Among the 29 patients with PR at T1, 44.8% showed either a CR, PR or SD as best response for T2. Of the 3 patients with progression as best response to first taxane exposure, 1 showed complete response at rechallenge.

3.7. Survival analyses

An exploratory analysis was conducted to determine PFS with taxanes in the rechallenge population. Median PFS for first taxane exposure was 12.4 months [0.5–86.6], and median PFS for taxane rechallenge was 5.7 months [0.1–99] (Fig. 4). In the 4 patients who had a second taxane rechallenge, median PFS of the second taxane rechallenge was 5.2 months [4–7.8]. PFS curves for HR+ and TNBC subgroups are shown in Supplementary data 4A-B.

As chemotherapy sequences were heterogeneous in the rechallenge population, we estimated the PFS2/PFS1 ratio, in which each patient is their own control. In the rechallenge population, PFS2/PFS1 ratio was >1.3 in 55.2% of patients, suggesting a certain effectiveness of the rechallenge with these chemotherapy drugs (Fig. 5A). We also examined PFS2/PFS1 ratio according to HR status (Fig. 5B).

Age at metastatic diagnosis, immunohistological subtype, metastatic history (relapse, or *de novo*), metastatic burden, visceral metastasis, previous use of taxanes in the adjuvant/neoadjuvant setting, adjuvant hormone therapy, and best response obtained at first taxane exposure were not significantly associated with PFS2 in univariate Cox analysis, and no factors were found to be significantly associated with PFS2/PFS1 ratio by logistic regression models as shown in Supplementary Data 5.

An exploratory analysis was conducted regarding OS. In the control population, median OS after first taxane exposure was 23.7 months [21.7–28.3] (28.8 months [23.7–35.2] in the HR + population and 17.3 months [13.6–21.7] in the TNBC population). In the rechallenge population, median OS after first taxane exposure was 46 months [38.8–56.4] (46 months [38.8–57.1] in the HR + population and 45.4 months [31.5–57.7] in the TNBC population), and median OS from taxane rechallenge was 11.6 months. The Kaplan-Meier curves are shown in Supplementary data 6.

4. Discussion

In this work, we report the outcome of 58 patients presenting with HER2-negative MBC and treated with a taxane rechallenge during their metastatic history. In our rechallenge population, taxanes in metastatic disease were frequently used as frontline chemotherapy (79.3% in the rechallenge population and 70.9% of the control population), consistent with general practice and international recommendations [1].

Pragmatically, even if MBC is considered to be chemosensitive, the therapeutic options are limited once the major cytotoxic drugs (anthracyclines, taxanes, eribulin, capecitabine) have been used, and have failed. However, real-life data [6] indicate that many patients still receive additional lines of treatment (such as gemcitabine, vinorelbine, platinum salts), and no clear current standard of care is available at this stage of the disease. Therefore, under certain circumstances, such as previous efficacy and tolerance or level of residual cumulative toxicity, it may lead clinicians to discuss the possible reintroduction of a previously used major cytotoxic drug, all the more so as it is routinely used in many other cancer types, like colorectal cancer [7].

Our results indicate that taxane rechallenge (mostly with weekly paclitaxel in our series) is not frequently used, since only 7.8% of the HER2-negative MBC population were concerned, but it yielded promising responses and disease control/clinical benefit rates. Moreover, our comparisons with “non rechallenged” patients (control population) could help the understand the decision-making factors in this strategy. Indeed, our analyses suggest that the decision to proceed with taxane rechallenge is driven both by certain clinical characteristics of the disease, and by the efficacy/safety profile of the first taxane exposure during the patient’s metastatic history. Compared to our control

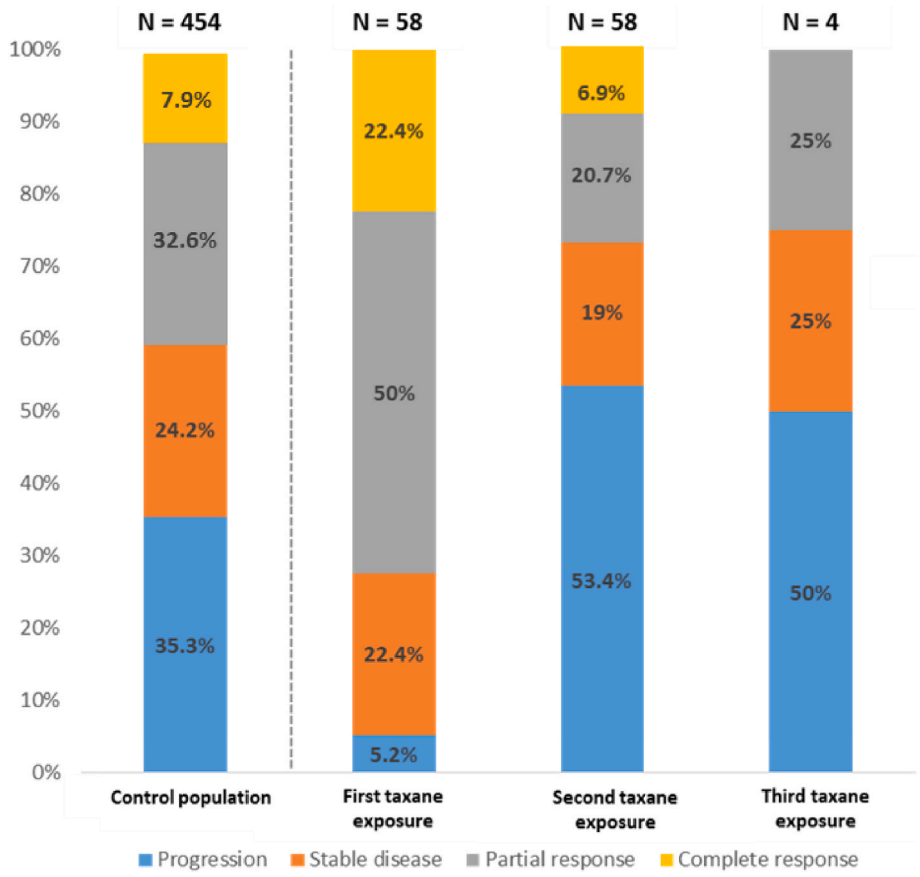

Fig. 2. Best response obtained in first, second and third taxane exposure in control and rechallenge population (cumulative bar graphs).

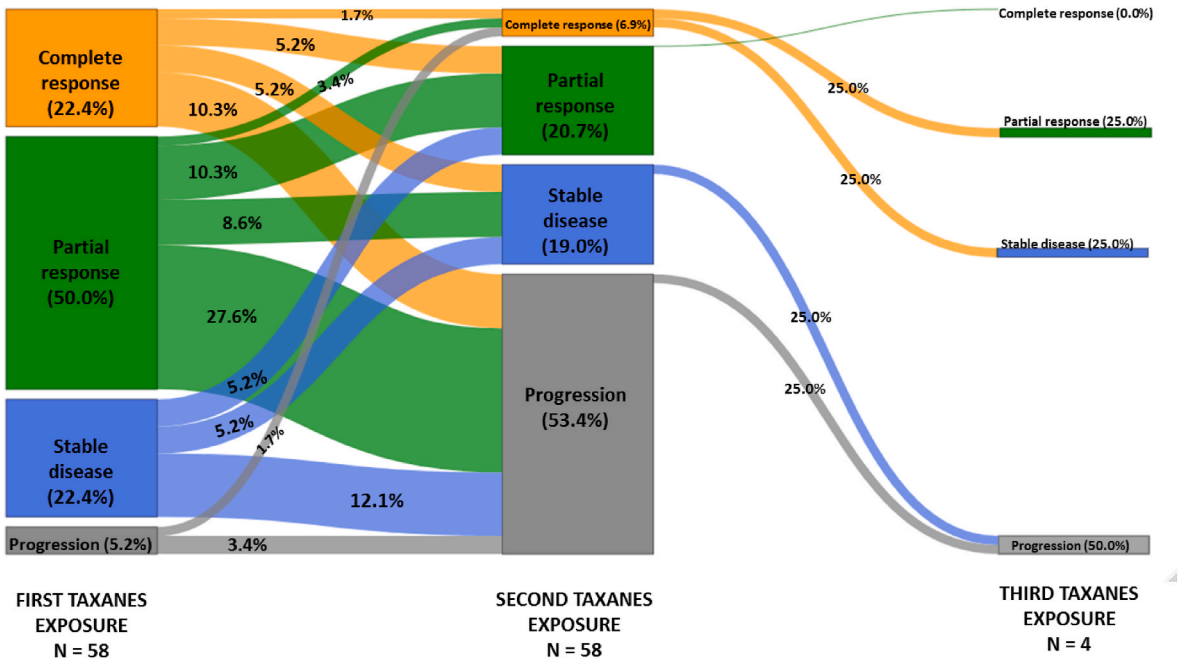

Fig. 3. Evolution of best therapeutic responses between first/second and third taxane exposure (sankey plots). This sankey plot illustrates the evolution of best therapeutic responses over time for each individual, from the initial response to taxanes (complete response, partial response, stable disease or progression) to the rechallenge response. T1, T2, T3: respectively first, second and third taxane exposure.

population of HER2-negative MBC, who were treated only once by taxanes, the rechallenge population appeared to be younger and in better general condition. This may contribute to the observed difference in OS, which seemed to be longer in patients who received taxane rechallenge. As is often the case in this type of retrospective study, it is difficult to determine whether the reintroduction of taxanes is the cause

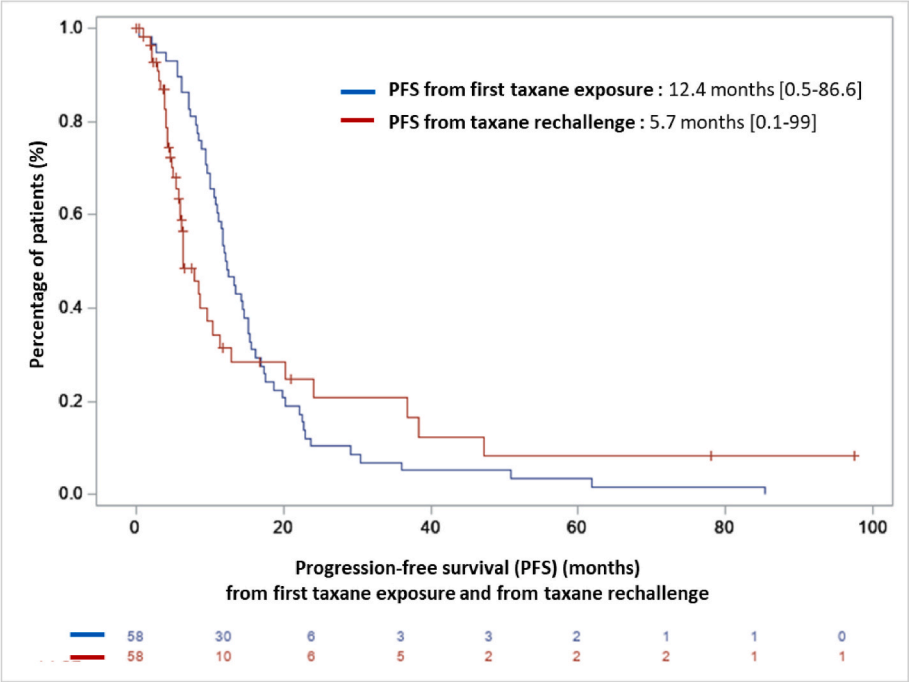

Fig. 4. PFS from first taxane exposure and second taxane exposure in the rechallenge population.

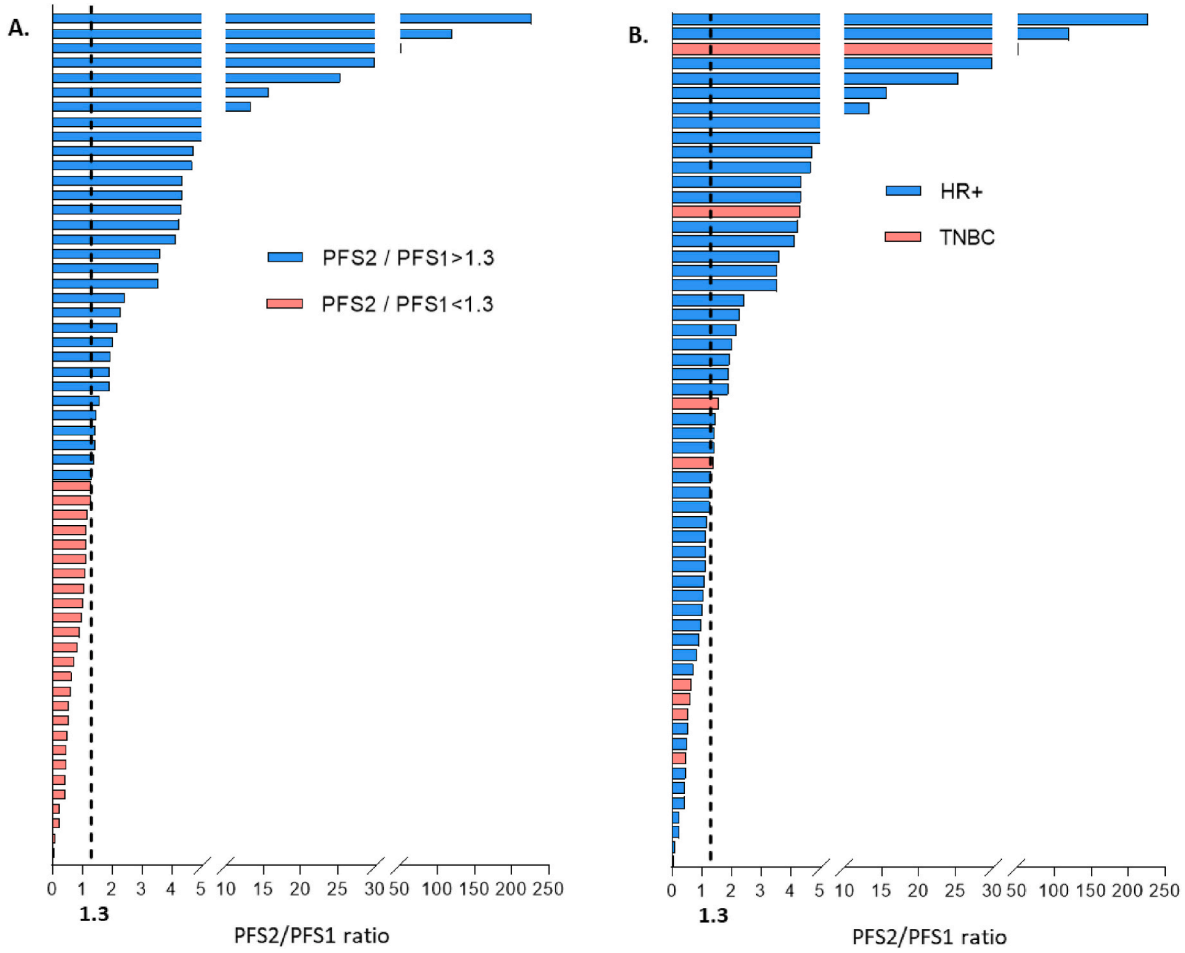

Fig. 5. A. Individual PFS2/PFS1 ratio, ordered by descending PFS2/PFS1 (waterfall plot). PFS2 was the PFS for taxane rechallenge and PFS1 the PFS for the prior line of treatment, and the ratio PFS2/PFS1 was compared to 1.3 [5]. Patients represented by blue bar have PFS2/PFS1 > 1.3. B: PFS2/PFS1 ratio according to HR status (waterfall plot).

or the consequence of longer survival. It is also challenging to unravel how the clinical and pathologic characteristics of both the disease and the patients might have influenced the efficacy of the treatment, or the possibility of rechallenge. Nonetheless, despite this possible bias, interestingly, at rechallenge, an objective response was observed in 27.6% of the population. The rechallenged population appeared to have been selected by clinicians according to first taxane exposure, which led to better tumor responses, and was more frequently discontinued for reasons other than disease progression (e.g. toxicity or chemotherapy break), compared to non-rechallenged population.

In the current literature, data suggesting the efficacy of taxane rechallenge is mostly available for taxanes that were previously used in the adjuvant or neoadjuvant settings, and rechallenged during metastatic relapse history. Regarding this clinical question, a recent analysis of the French ESME cohort evaluated the efficacy of taxane rechallenge in early metastatic relapse (<24 months) in 23,501 patients treated for HER2-negative MBC between 2008 and 2017, and reported that patients with taxane rechallenge had a similar time to relapse compared to those treated with other chemotherapies [8]. A study by Guo et al. [9] reported an ORR of 48.6% with taxanes as first line for MBC, and 28.2% with taxanes as later lines, in 106 patients who had previously received taxanes in the (neo)adjuvant setting. No difference was found in response rates according to the type of taxane, but the presence of visceral metastasis and the length of the disease-free interval (more or less than two years) were significantly associated with tumor response. Another retrospective study published in 2016 [10] found an ORR of 58.5% (with 12% having complete response) in 191 patients previously exposed to taxanes during adjuvant chemotherapy and who received a taxane-based regimen at frontline metastatic treatment. In the same study, for patients receiving a taxane-based regimen as a second or later line of treatment, ORRs were above 40%. The response rate of patients who had received the same taxane both times were similar to those who had received a different taxane.

Fewer reports have described, as in our study, taxane rechallenge during a strictly metastatic setting. The aforementioned study by Guo et al. reported a strictly metastatic taxane rechallenge in only 7 patients, and the small number of patients did not incite the authors to recommend the strategy. A larger retrospective study was conducted in 2012 [11] and reported outcomes of docetaxel-only rechallenge in 72 MBC patients. Importantly, this study was conducted in a highly selected patient population (objective response or stable disease with a previous line of docetaxel in the metastatic setting, discontinuation for a reason other than progression, and minimal docetaxel-free interval of 3 months). Out of 72 patients, only 33 were evaluated according to the RECIST criteria: 42.5% of patients were considered to have PR, and 33.5% SD, which was less than observed in our study.

Rechallenge can be attempted with the same taxane, or a different taxane. In the literature, docetaxel rechallenge after paclitaxel exposure in a cohort of 24 patients showed RRs around 20%, suggesting cross-resistance between the two agents [12]. In our study, we included all patients treated with taxane rechallenge, in order to accurately describe current practice. Paclitaxel was the most frequently used taxane for rechallenge in our series, and its effectiveness in this situation did not appear to depend on the type of taxane used during first exposure in metastatic disease.

These results are consistent with the reported moderate efficacy of a second, different taxane treatment in some patients presenting with various cancer types and who became refractory to a first taxane treatment, when paclitaxel and docetaxel were used sequentially in the same patients [13–16].

Taxanes, especially paclitaxel given in a weekly schedule, have an acceptable and well-known tolerance profile that enables their prescription for largely pre-treated and frail patients. Their use is sometimes limited by cumulative toxicity, especially peripheral neuropathy, and our cohort is no exception: 43.1% stopped the first taxane treatment, at least partially following grade III toxicity (25.9% following grade III peripheral neuropathy). These findings are in agreement with those of the cohort reported by Toulmonde et al., in which 32% of patients experienced grade 3/4 toxicity (due to the exclusive use of docetaxel, mostly neutropenia (17%) and fluid retention (10%)). Regarding the safety profile of taxane rechallenge, our reports of adverse events corroborate the real-life routine experience with cases of peripheral neuropathy leading to treatment discontinuation for 25.9% of patients during first taxane exposure, and 3.5% of patients during rechallenge.

In our study, PFS and OS were exploratory. In our rechallenge population, median PFS after first taxane exposure was 12.4 months, and median PFS after taxane rechallenge was 5.7 months; median OS was 11.6 months. Interestingly, these results observed in a "all-comer" rechallenged population are consistent with those of Toulmonde et al., who reported a median time to progression in a very highly selected rechallenge population of 5.7 months, and median OS of 10.2 months. To appreciate the benefit of rechallenge for a given patient, we evaluated the PFS2/PFS1 ratio, which exceeded 1.3 for more than half of the patients, thereby suggesting clinically relevant activity in a majority of rechallenged patients. It will be interesting to see in the future if such cytotoxic chemotherapy rechallenge strategies retain their interest in the era of the development of new treatments such as antibody drug conjugates.

In the rechallenge population, taxane reintroduction occurred after a median of 2 lines of treatment, but with large differences between patients [0 to 8 lines], illustrating two different patient trajectories, namely: reintroduction of taxanes after progression under maintenance therapy, and rechallenge following failure of a few subsequent lines of treatment. From our observations, we identified several reasons that could contribute to taxane discontinuation, either at first or second exposure, such as good or excellent response to treatment, or good response paired with undeniable toxicity, thus inciting the physician to opt for a therapeutic break or maintenance therapy (77.6%). Significant toxicity (grade II or even III-IV) could lead to treatment discontinuation, as well as disease progression while patients were being treated with taxane. Logically, in our rechallenge population, disease progression was the main reason for discontinuation during the first treatment for only 6.9% of patients.

We believe that our results are interesting in the context of the existing literature. Indeed, to the best of our knowledge, this retrospective work presents the largest "real-life" population of either paclitaxel or docetaxel rechallenge in a MBC population. Although taxane rechallenge is a rather marginal practice, the local database and restricted population enabled us to delve deeper into the details of the therapeutic strategy, and to carefully examine treatment milestones. We observed that taxane rechallenge is an interesting option for some highly pretreated patients. However, the retrospective data collection and the small population limit the generalizability of the findings. Another limitation of our study is its duration over time, and the inclusion of patients with tumors treated according to different standard of care, depending on the era (with for instance the recent arrival of CDK4/6 inhibitors for ER+/HER2- MBC). Regarding this last point, it should be noted that in our study population, only a small fraction of patients with ER+/HER2-negative tumors received endocrine therapy as first-line treatment for MBC (16%). This corresponds to the former local practice in our center, which favored chemotherapy followed by endocrine maintenance therapy, and therefore does not reflect the real world data published during this period [17]. However, we believe that this does not alter the interpretation of the taxane rechallenge results. The heterogeneity of the population also complicates the interpretation, but we investigated the PFS2/PFS1 ratio in order to evaluate each patient as their own control.

In conclusion, this retrospective analysis supports the pragmatic practice of retreating MBC patients with taxanes, especially when these drugs have shown previous clinical activity earlier in the disease course, and/or when they were discontinued for reasons other than progression.

Declaration of competing interest

The authors declare that they have no conflicts of interest with the contents of this article.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.breast.2023.01.015.

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