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Original article

Chemotherapy versus endocrine therapy as first-line treatment in patients with luminal-like HER2-negative metastatic breast cancer: A propensity score analysis

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ABSTRACT

Background: According to current guidelines, endocrine therapy (ET) is recommended as first-line treatment of luminal-like metastatic breast cancer (MBC), whereas chemotherapy (CT) should be considered in presence of life-threatening disease. In daily practice, CT is often used outside of this clinical circumstance. Factors influencing first-line choice and the relative impact on outcome are unknown.

Methods: A consecutive series of luminal-like HER2-negative MBC patients treated from 2004 to 2014 was analyzed to test the association of disease- and patient-related factors with the choice of first-line treatment (ET vs. CT). A propensity score method was used to estimate impact of first-line strategy on outcome.

Results: Of 604 consecutive luminal-like MBC patients identified, 158 cases were excluded due to unknown or positive HER2-status. Among 446 HER2-negative cases, 171 (38%) received first-line CT. On multivariate analysis, the only factors significantly associated with lower CT use were old age (OR 0.25, 95%C.I. 0.13–0.49) or presence of bone metastases only (OR 0.26, 95%C.I. 0.13–0.53). In propensity score matched population, no differences were observed between CT and ET as first-line treatment either in terms of overall survival (37.5 months and 33.4 months respectively, log-rank test, P = 0.62) or progression-free survival (13.3 months and 9.9 months respectively, log-rank test, P = 0.92).

Conclusions: High percentage of patients with luminal-like MBC received CT as first-line therapy in real-life. The choice was mainly driven by age and site of metastases. With the limitations of a non-randomized comparison, no differences on patients' outcome were observed depending on the first-line strategy.

1. Introduction

Breast cancer (BC) is the most common type of cancer in women, with 40,450 estimated deaths in the United States, in 2016 [1]. Metastatic disease occurs in approximately 20–50% of patients with early BC history and in 6–10% of newly diagnosed BC cases [2]. Overall survival (OS) of women with metastatic breast cancer (MBC) ranges from a few months to many years accordingly with the BC subtype [3,4], while almost none are definitely cured.

The optimal sequence of systemic agents for MBC remains unknown. Considerations about tumor burden, symptoms, expected toxicities, quality of life, and patient's preferences drive clinicians' decision-making process. Hormone receptor status and HER2

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status are the only validated tumor characteristics that predict the benefit from specific treatments, but there is no evidence about the utility of making therapeutic choices on the basis of tumor subtypes (i.e., luminal A or luminal B or triple negative) [5,6]. Recommendation for endocrine therapy (ET) versus chemotherapy (CT) as first-line treatment of hormone receptor-positive MBC is reported by the main international guidelines [6,7]. The use of ET is supported by data showing a therapeutic benefit with less toxicity and better quality of life in comparison to CT [6–9]. Nevertheless, it is generally thought that CT is associated with greater and earlier tumor response, especially in case of high burden of disease. For patients with hormone receptor-positive and HER2-positive disease chemotherapy plus HER2-targeted therapy was strongly recommended, except for highly selected cases for whom clinicians may offer endocrine therapy [10]. On the contrary, for women with hormone receptor-positive HER2-negative disease the question of whether to use CT or ET as first-line treatment MBC remains, to date, partially unresolved.

Aim of this study was to describe the use of CT and ET regimens as first-line treatment of women with hormone receptor-positive HER2-negative MBC, outside the setting of clinical trials, in real world scenario.

In particular, two main issues were taken into consideration: (i) to test the association between patient- or disease-related factors and first-line treatment choice (ET vs. CT); and (ii) to explore the influence of first-line treatment choice (ET vs. CT) in terms of outcome.

2. Methods

2.1. Study design

This retrospective study analyzed a series of 604 consecutive patients with luminal-like (i.e. hormone receptor-positive) HER2-negative MBC treated at the University Hospitals of Naples and Udine, Italy, between 2004 and 2014. The study population included women with advanced BC, either newly diagnosed or recurrent. Patients with HER2-positive (or HER2-unknown) disease, with second primary tumors and those who did not receive any active treatment for metastatic disease were excluded. Demographic and clinico-pathological data were extracted from electronic medical records and treated according to strict privacy standards.

We collected data about CT and ET focusing on first-line choice. Among patients treated with first-line CT, the subsequent administration of maintenance ET in patients without disease progression at the completion of CT (CT→ET) was also recorded.

According to current guidelines [11], the cutoff point of 1% was used to define estrogen receptor (ER) and/or progesterone receptor (PR) positivity. The cutoff value for the immunohistochemically determined Ki-67 index to distinguish luminal B was 14% [12]. The following BC subtypes were defined: “luminal A” (HER2-negative, Ki-67 $\leq$ 14%), “luminal B” (HER2-negative, Ki-67 > 14%).

OS was defined as the time between first-line treatment initiation and death from any cause. Progression Free Survival (PFS) was defined as the time between treatment initiation and tumor progression or death from any cause. The date of progression was identified as the date at which progression was first evident (e.g. imaging, biochemical examination, clinical visit).

The following variables were studied as patient- or disease-related variables potentially associated with first-line choice and/or as prognostic factors: age ($\geq$70 vs. <70 years old), body mass index (BMI>25 vs. $\leq$25), performance status (PS) according to the Eastern Cooperative Oncology Group (ECOG) scale (PS ECOG$\geq$2 vs. <2), BC subtypes (luminal B vs. luminal A), onset of MBC (*de novo* advanced vs. recurrent disease), number of metastatic sites ($\geq$2 vs. 1), previous neo-/adjuvant ET and/or CT (yes vs. no), visceral involvement (yes vs. no), bone only disease (yes vs. no), lung (yes vs. no), liver (yes vs. no), and central nervous system (CNS, yes vs. no) metastases.

2.2. Statistical analysis

Patients' demographic and clinico-pathological characteristics were summarized through descriptive analysis. Continuous variables were reported through median and interquartile range, whereas categorical variables were described through frequency distribution. Factors influencing the prescription of a first-line ET vs. CT were investigated through uni- and multivariate logistic regression with odds ratio (OR) calculation. Prognostic factors in terms of OS and PFS among different treatment subgroups were tested by Cox regression with 95% confidence interval (95%C.I.) both in uni- and multivariate models. To assess the different impact on outcome measures of first-line treatment choice, population was sampled and balanced using propensity score matching (PSM), computed taking in consideration age and performance status at first-line, breast cancer subtypes, onset of advanced disease, presence of visceral metastases, lung and liver metastases and number of visceral sites involved. The matching approach was 1:1 nearest neighbor with caliber of 20%. Differences in survival were tested by log-rank test and represented by Kaplan-Meier estimator plot. A landmark analysis with 6 months threshold was performed in order to minimize the bias in the exploratory analysis of the impact of ET maintenance after CT on outcome: patients who progressed before 6 months had a very low chance of receiving ET maintenance and their inclusion in the comparison would have obviously biased the comparison in favor of the group of patients receiving maintenance.

3. Results

Of 604 consecutive luminal-like MBC patients identified, 158 cases were excluded due to unknown or positive HER2-status. Among 446 HER2-negative cases, first-line CT was chosen in 38% (171/446) of patients. Median age of women treated with first-line ET and CT was 68 (range 39–92) and 58 (range 30–81) years, respectively. Baseline characteristics of patients according to first-line treatment are summarized in Table 1A.

3.1. Association between patient- or disease-related factors and first-line treatment choice

The individual characteristics of CT and ET groups are showed in Table 1A. Patients with potentially more unfavorable characteristics such as younger age, good performance status, higher number of metastatic sites and a greater visceral involvement basically received CT more often than ET. No differences were observed according to the center (Udine vs. Napoli). On multivariate analysis, age $\geq$70 years (OR 0.25, 95%C.I. 0.13–0.49, P < 0.0001), or bone only disease (OR 0.26, 95%C.I. 0.13–0.53, P < 0.0001) were associated with lower use of CT as first treatment. A trend was observed for performance status (OR 0.48, 95%C.I. 0.23–1.00, P 0.05). Uni- and multivariate results are showed in Table 2. Of note, in the subgroup of patients with a recurrent MBC excluding *de novo* diagnosis, relapsing within 5 years from breast cancer surgery was not significantly associated with first-line regimen (data not shown).

In a subset of patients, maintenance therapy with ET was given after initial CT regimen in absence of progressive disease (CT→ET group). Namely, 88 patients received CT whereas 83 received CT→ET. Baseline characteristics of patients according to CT strategy

Table 1
Baseline characteristics of the endocrine therapy and chemotherapy groups. Bold values indicate statistically significant results.

Characteristic	A- whole study population			B- population selected by propensity score matching[a]		
	Endocrine therapy $N = 275$	Chemotherapy $N = 171$		Endocrine therapy $N = 99$	Chemotherapy $N = 99$	
	N (%)	*N (%)*	*P value*	*N (%)*	*N (%)*	*P value*
Institution						
Udine	211 (77%)	127 (74%)	0.56	72 (73%)	72 (73%)	1.00
Napoli	64 (23%)	44 (26%)		27 (27%)	27 (27%)	
Age (3 missing)						
<70	156 (57%)	145 (86%)	**<0.0001**	76 (77%)	78 (79%)	0.73
≥70	118 (43%)	24 (14%)		23 (23%)	21 (21%)	
Performance status						
0/1	217 (79%)	150 (88%)	**0.02**	82 (83%)	84 (85%)	0.70
2	58 (21%)	21 (12%)		17 (17%)	15 (15%)	
Subtype (54 missing)						
Luminal A	77 (32%)	32 (22%)	**0.03**	23 (23%)	23 (23%)	1.00
Luminal B	167 (68%)	116 (78%)		76 (77%)	76 (77%)	
De novo advanced disease						
	93 (34%)	55 (32%)	0.72	33 (33%)	29 (29%)	0.54
Bone only						
	136 (49%)	35 (20%)	**<0.0001**	32 (32%)	21 (21%)	0.08
Visceral metastases						
	84 (30%)	99 (58%)	**<0.0001**	47 (47%)	50 (50%)	0.67
Liver metastases						
	38 (14%)	53 (31%)	**<0.0001**	21 (21%)	24 (24%)	0.64
Lung metastases						
	34 (12%)	43 (25%)	**0.001**	23 (23%)	22 (22%)	0.84
CNS metastases						
	3 (1%)	4 (2%)	0.31	0 (0%)	1 (1%)	0.32
Number of sites						
1	218 (79%)	101 (59%)	**<0.0001**	67 (68%)	65 (65%)	0.76
>1	57 (21%)	70 (41%)		32 (32%)	34 (34%)	

[a] Matched by age, performance status, tumor subtype (Luminal A, Luminal B), onset of advanced disease, presence of visceral metastases, presence of liver metastases, presence of lung metastases, number of metastatic sites.

Table 2
Chemotherapy use by tumor and patient characteristics (vs. endocrine therapy). (BMI, Body Mass Index; CI, Confidence Interval; CNS, Central Nervous System; CT, Chemotherapy; ECOG, Eastern Cooperative Oncology Group; ET, Endocrine Therapy; OR, Odds Ratio; NA, not applicable due to multicollinearity). Bold values indicate statistically significant results.

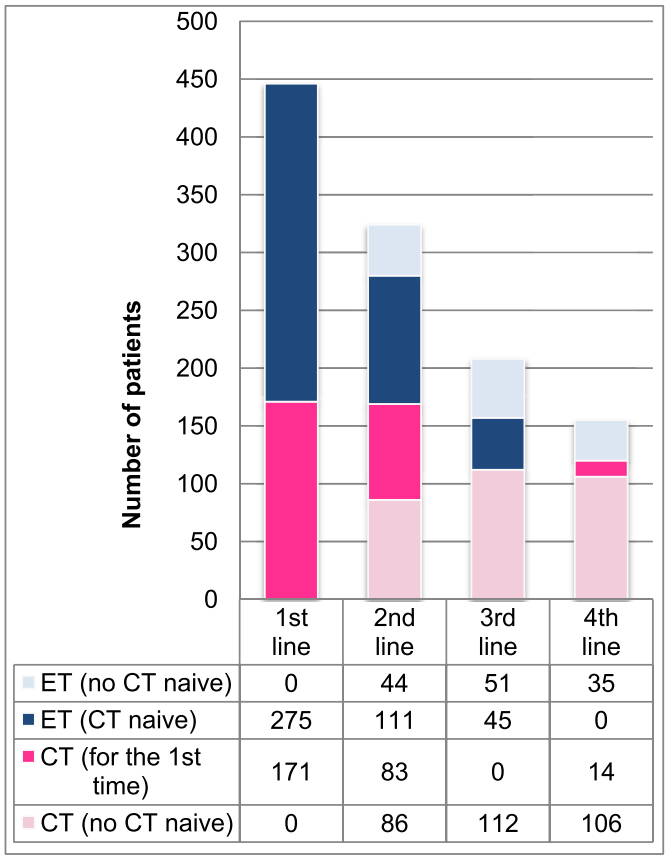
	Chemotherapy			
	Univariate		Multivariate	
	OR [CI 95%]	P value	OR [CI 95%]	P value
Subtype-Luminal B	1.67 [1.04–2.69]	0.03	1.61 [0.85–3.05]	0.14
BMI >25	0.57 [0.37–0.89]	0.01	**0.62 [0.37–1.07]**	**0.09**
ECOG performance status >1	0.52 [0.30–0.90]	0.02	0.48 [0.23–1.00]	0.05
Age ≥70	0.22 [0.13–0.36]	<0.0001	**0.25 [0.13–0.49]**	**<0.0001**
CT naïve	0.60 [0.41–0.88]	0.008	0.93 [0.54–1.60]	0.80
ET naïve	1.35 [0.97–1.88]	0.07	–	–
De novo advanced disease	0.93 [0.62–1.39]	0.74	-	-
Bone only	0.26 [0.17–0.41]	<0.0001	**0.26 [0.13–0.53]**	**<0.0001**
Liver metastases	2.79 [1.74–4.47]	<0.0001	1.49 [0.75–2.98]	0.26
Lung metastases	2.37 [1.44–3.90]	0.001	1.35 [0.64–2.84]	0.43
CNS metastases	2.16 [0.48–9.79]	0.32	–	–
Visceral metastases	3.13 [2.10–4.65]	<0.0001	NA	NA
Number of sites>1	2.65 [1.74–4.04]	<0.0001	1.30 [0.63–2.68]	0.47

were summarized in Supplementary Table S1 (Supplementary data). Disease subtype, metastatic sites, onset of advanced disease, BMI, age and ECOG performance status were not associated with ET maintenance. On multivariate analysis, patients not having received previous (neo- or adjuvant) ET were more likely to receive an ET maintenance treatment (OR 3.69, 95%C.I. 1.94–7.02; $P < 0.0001$). Uni- and multivariate results were showed in Supplementary Table S2 (Supplementary data). Beyond first-line, clinicians choose to introduce chemotherapy or continue with endocrine regimens in the same proportion. Some women received ET after one or more chemotherapy lines. Description of therapeutic strategy along subsequent lines is presented in Fig. 1.

3.2. Outcome according to first-line treatment choice (ET vs. CT)

Median follow-up was 52 months. In the whole population median OS was 36 months, while median PFS was 10.5 months. In patients treated with CT as first-line treatment, median OS was 36.6 months and median PFS was 11.6 months. Among cases treated with ET as first-line treatment, median OS was 35 months and median PFS was 9.6 months. Comparisons of PFS and OS between different treatment groups are presented in Fig. 2A.

Clinico-pathological factors were evaluated to test the association with outcome measures according to first-line therapy (Table 3). In multivariate analysis, OS was shorter for patients with



	1st line	2nd line	3rd line	4th line
ET (no CT naive)	0	44	51	35
ET (CT naive)	275	111	45	0
CT (for the 1st time)	171	83	0	14
CT (no CT naive)	0	86	112	106

Fig. 1. Description of therapeutic strategy (CT, chemotherapy; ET, endocrine therapy). The following subgroups were defined: choice of CT or ET for patients that have never received a CT line for MBC ["CT (for the first time)" and "ET (CT naive)" respectively], choice of CT or ET for patients that have already received a CT line for MBC ["CT (no CT naive)" and "ET (no CT naive)" respectively].

several metastatic sites (HR 1.91, 95%C.I. 1.29–2.84); duration of OS was associated with number of therapeutic lines for MBC (HR 0.84, 95%C.I. 0.77–0.92) in patients treated with CT. In patients treated with ET, shorter OS was associated with luminal B subtype (HR 1.86, 95%C.I. 1.27–2.72), poor performance status (HR 1.96, 95%C.I. 1.31–2.95), age ≥70 (HR 1.83, 95%C.I. 1.31–2.58), and multiple metastatic sites (HR 1.91, 95%C.I. 1.23–2.97).

In multivariate analysis, shorter PFS was associated with multiple metastatic sites (HR 1.52, 95%C.I. 1.08–2.12) in patients treated with CT. In patients treated with ET, shorter PFS was associated with luminal B subtype (HR 1.82, 95%C.I. 1.32–2.50); longer PFS was associated with being ET naïve (HR 0.65, 95%C.I. 0.49–0.86).

PSM selected a subgroup of 198 patients (99 treated with ET and 99 treated with CT). Baseline characteristics of matched patients by systemic treatment are summarized in Table 1B. The analysis of the matched subset showed similar outcome in patients treated with CT vs. ET, either in terms of OS (37.5 months and 33.4 months respectively, log-rank test, P = 0.62) or PFS (13.3 months and 9.9 months respectively, log-rank test, P = 0.92). Comparisons of PFS and OS between matched groups are presented in Fig. 2B.

To explore the impact of ET maintenance on outcome, PFS and OS were calculated in a secondary landmark analysis, excluding patients progressing within 6 months while on CT. Restricting the analysis to 119 patients (39 treated with CT alone and 80 treated with CT→ET) PFS was significantly improved by ET maintenance (median 17.0 vs. 12.2 months, P = 0.0075), on the contrary OS was not statistically different (median 47.7 vs. 47.2 months, P = 0.57). Comparisons of PFS and OS between different treatment groups (CT vs. CT→ET) are presented in Fig. S1 (Supplementary data).

4. Discussion

Our study showed that a CT-based regimen was the preferred first-line therapy in more than one-thirds of the patients with luminal-like HER2-negative MBC treated in routine clinical practice. Interestingly, only two factors (i.e. age and bone only metastatic involvement) had an impact on the therapeutic decision making process.

After matching for covariates that significantly differed between the two study cohorts of patients (those receiving CT vs. ET as first-line), receiving CT did not significantly improve survival compared to ET.

Current guidelines suggest that ET should be the preferred first-line treatment for luminal-like MBC. However, higher response rates and faster response associated with CT may induce clinicians to prescribe first-line CT to patients with rapidly progressive, symptomatic disease or visceral metastases at risk for end-organ dysfunction.

Few studies explored clinician behavior approaching first-line of treatment in MBC patients and their data are consistent with our findings [13–15].

Patients with HER2-positive, hormone receptor-positive MBC were excluded by analysis. Chemotherapy, combined with HER2-targeted therapy is the preferred first-line approach. Actually, few studies compared ET with or without anti-HER2 drugs with no studies directly comparing ET versus CT both combined with HER2-targeted therapy [16,17]. Patients with HER2-positive luminal-like MBC were included in first-line CT plus anti-HER2 trials. In CLEOPATRA trial, for example, about 48% (388/808) of patients had luminal-like disease and exploratory analyses in predefined subgroups showed a consistent benefit with pertuzumab also in ER-positive population (HR 0.71, 95% C.I. 0.53–0.96) [18]. Initial therapy with endocrine agents is usually restricted to women who are not eligible for CT or for whom CT is not deemed to be immediately necessary for disease control.

Intriguingly, our data showed that Ki-67 status, previous treatment for early disease and presence of lung, liver or CNS metastases were not associated with treatment choice. Presence of bone metastases was the only disease characteristic associated with choice of first-line treatment. Results about molecular subtypes could be partly affected by changes in evidence over time.

In daily clinical practice, switching to maintenance ET during first-line CT (usually at least after 6 months of CT) is a commonly employed strategy aiming to reduce treatment side effects without compromising OS [19–21]. In our series, the lack of previous neo-adjuvant or adjuvant ET was associated with higher use of maintenance ET.

Nonetheless, due to the small sample size, a note of caution is needed in interpreting these findings.

With the limitations of a non-randomized comparison, no significant differences were seen in terms of outcome depending on the first-line choice. Recommendation of initiating ET was essentially based on results from a systematic review and its updates [22], published in the Cochrane Database of Systematic Reviews, which compared starting treatment with CT versus ET. Pooled analysis of data from 8 trials showed a significant advantage in terms of response rate for CT over ET. Of note, no significant difference was observed in terms of OS (HR 0.94, with a test for heterogeneity giving a P value of 0.1) and, on subset analysis, there was no obvious trend to suggest an effect of age, menopausal status or pattern of metastatic disease on the efficacy of either therapy. Only 10 studies were available to provide information on response to treatment and outcome. Notably, a major limitation to these

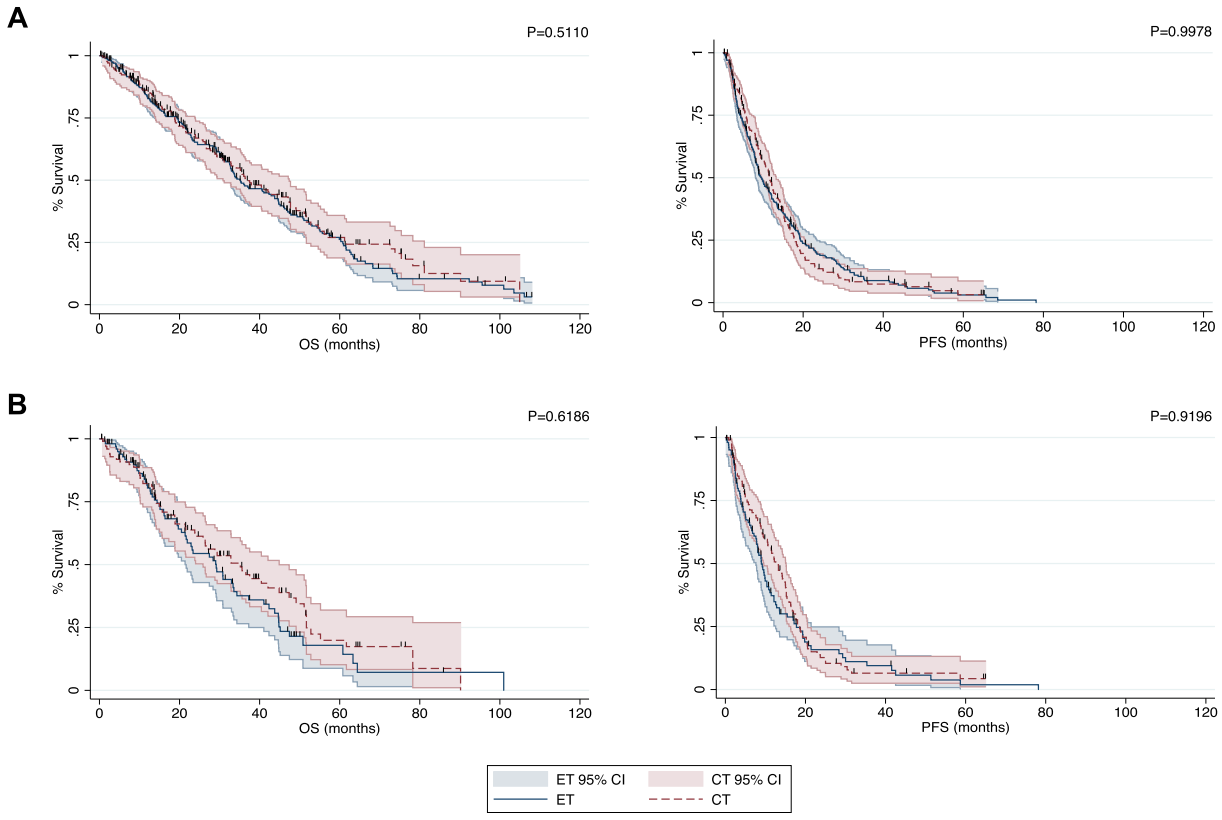


Fig. 2. Outcome according to first-line treatment choice. Kaplan-Meier estimator plot comparing prognosis of chemo versus endocrine treated patients in terms of overall survival and progression free survival, both in the complete dataset (panel A) and after propensity score matching (panel B). (CT, chemotherapy; ET, endocrine therapy; OS, Overall Survival; PFS, Progression Free Survival).

Table 3
Survival prior to matching: prognosis factors in univariate and multivariate (BMI, Body Mass Index; CNS, Central Nervous System; CI, Confidence Interval; CT, Chemotherapy; ECOG, Eastern Cooperative Oncology Group; ET, Endocrine Therapy; HR, Hazard Ratio; MBC, Metastatic Breast Cancer). Bold values indicate statistically significant results.

		Chemotherapy				Endocrine therapy			
		Univariate		Multivariate		Univariate		Multivariate	
		HR [CI 95%]	P value	HR [CI 95%]	P value	HR [CI 95%]	P value	HR [CI 95%]	P value
Overall survival	Subtype-Luminal B	1.14 [0.69–1.88]	0.61			1.93 [1.33–2.81]	0.001	**1.86 [1.27–2.72]**	**0.001**
	BMI >25	1.39 [0.88–2.20]	0.16			0.99 [0.69–1.42]	0.95		
	ECOG performance status >1	1.22 [0.63–2.36]	0.55			1.93 [1.31–1.42]	0.001	**1.96 [1.31–2.95]**	**0.001**
	Age ≥70	1.67 [0.98–2.86]	0.06			2.04 [1.50–2.78]	<0.0001	**1.83 [1.31–2.58]**	**<0.0001**
	CT naïve	0.61 [0.41–0.92]	0.02	0.85 [0.44–1.62]	0.61	0.96 [0.71–1.30]	0.78		
	ET naïve	0.63 [0.42–0.95]	0.03	0.67 [0.33–1.36]	0.27	0.76 [0.56–1.04]	0.08		
	De novo advanced disease	0.60 [0.39–0.93]	0.02	0.95 [0.44–2.04]	0.89	0.89 [0.67–1.17]	0.39		
	Bone only	0.97 [0.62–1.53]	0.90			0.82 [0.61–1.12]	0.21		
	Liver metastases	1.39 [0.92–2.09]	0.12			2.97 [1.98–4.45]	<0.0001	**1.77 [1.06–2.96]**	**0.03**
	Lung metastases	1.41 [0.90–2.18]	0.13			1.56 [0.95–2.56]	0.08		
	CNS metastases	1.63 [0.40–6.62]	0.50			39.69 [11.26–139.9]	<0.0001	NA	NA
	Visceral metastases	1.33 [0.90–1.98]	0.15			2.11 [1.52–2.91]	<0.0001	NA	NA
	Number of sites >1	1.85 [1.26–2.73]	0.002	**1.91 [1.29–2.84]**	**0.001**	2.80 [1.96–3.98]	<0.0001	**1.91 [1.23–2.97]**	**0.004**
	Number of lines for MBC	0.86 [0.79–0.93]	<0.0001	**0.84 [0.77–0.92]**	<0.0001	0.93 [0.87–0.99]	0.03	0.97 [0.89–1.05]	0.48
Progression free survival	Subtype-Luminal B	1.15 [0.75–1.77]	0.51			1.77 [1.30–2.43]	<0.0001	**1.82 [1.32–2.50]**	**<0.0001**
	BMI >25	1.25 [0.86–1.81]	0.25			0.94 [0.69–1.30]	0.72		
	ECOG Performance status >1	0.88 [0.53–1.46]	0.63			1.31 [0.94–1.83]	0.11		
	Age ≥70	1.49 [0.94–2.38]	0.09			1.24 [0.95–1.62]	0.11		
	CT naive	0.66 [0.48–0.92]	0.01	0.89 [0.53–1.51]	0.67	0.77 [0.59–1.00]	0.05		
	ET naive	0.61 [0.44–0.85]	0.004	0.55 [0.29–1.04]	0.07	0.75 [0.58–0.98]	0.04	**0.65 [0.49–0.86]**	**0.003**
	De novo advanced disease	0.67 [0.47–0.95]	0.03	1.21 [0.61–2.42]	0.58	0.89 [0.67–1.17]	0.39		
	Bone only	0.94 [0.63–1.39]	0.75			0.87 [0.67–1.13]	0.31		
	Liver metastases	1.40 [0.99–1.99]	0.06			2.19 [1.51–3.17]	<0.0001	1.48 [0.94–2.31]	0.08
	Lung metastases	1.27 [0.87–1.84]	0.21			1.02 [0.68–1.53]	0.91		
	CNS metastases	0.56 [0.14–2.27]	0.42			7.44 [2.35–23.60]	0.001	NA	NA
	Visceral metastases	1.24 [0.89–1.72]	0.20			1.53 [1.15–2.03]	0.003	NA	NA
	Number of sites >1	1.44 [1.03–2.01]	0.03	**1.52 [1.08–2.12]**	**0.02**	1.82 [1.31–2.53]	<0.0001	1.44 [0.96–2.18]	0.08

findings is that most patients in these trials had tumors of unknown hormone receptor status, since the predictive value of this characteristic on response to ET was not yet appreciated.

Data from our unselected real world population confirmed no significant difference in terms of survival (i.e. both PFS and OS) for CT versus ET. This result derived from analysis by a propensity score matching, applied to minimize confounding and indication bias. Even though propensity score matching simulates randomization, it is capable to correct only known confounders. Because of this, it cannot be considered a reliable substitute for randomization. Data on response were not evaluated due to the retrospective design of the study.

It is therefore difficult to identify potential predictive factors of benefit from ET or CT. Of interest, hazard ratio analysis showed that status of Ki-67 (luminal B vs. luminal A) was relevant only for ET suggesting a different impact of this variable between two different cohorts of treatment. Another noteworthy issue is the impact of previous (neo-adjuvant) therapies in the treatment choice and in terms of outcome. If on one hand, being ET and CT naïve as well as the time to relapse did not influence first-line treatment choice, on the other hand being ET naïve was associated with better PFS in ET treatment cohorts. Patients ET naïve were, for the most part, those with *de novo* advanced disease. Disease burden was associated with worse survival in both cohorts.

Among patients treated with first-line CT, better outcome was observed in those that received ET maintenance and it might be hypothesized that this part of the treatment could have improved prognosis of first-line CT group. In fact, restricting the analysis to patients who not underwent disease progression within 6 months after starting CT, PFS was improved by ET maintenance.

5. Conclusion

This study is based on an analysis of a large series of BC patients treated in two high-volume academic centers. Data describe a "real-life" scenario taking in consideration clinical records starting from 2004 and therefore focusing on modern regimens, differently from previous similar studies that were limited to cohorts treated between 1990 and early 2000s. On the other hand, the present study did not analyze objective response (which could be questionable when considered retrospectively) and no quality of life data were available. Propensity score analysis attempted to reduce but not neutralized limitations of a non-randomized study.

Nonetheless, retrospective observational trial offers an interesting insight on treatment strategy for luminal-like MBC. Differences between endocrine therapy and chemotherapy have never been observed in prospective dedicated trials and in a meta-analysis. In addition, no new generation trials directly compared endocrine therapy versus chemotherapy. Therefore, development of endocrine treatment ran parallel but distinct to chemotherapy, making choice of sequence complex in everyday practice.

In addition, as already shown in a recent paper in different setting of BC patients [23], depth analysis of treatment population characteristics in a real-life series provides useful information to interpret guideline adherence, evaluate patterns of care and motivate quality of care improvement.

Declaration of interest

The authors declare that they have no competing interests.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.breast.2016.10.021.

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