

Original article

Disease management patterns for postmenopausal women in Europe with hormone-receptor-positive, human epidermal growth factor receptor-2 negative advanced breast cancer

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Abstract
Background:

International guidelines for hormone-receptor-positive (HR⁺), human epidermal growth factor receptor-2 negative (HER2⁻) advanced breast cancer (BC) recommend sequential lines of hormonal therapy (HT), and only recommend chemotherapy for patients with extensive visceral involvement or rapidly progressive disease. This study evaluated actual physician-reported treatments for advanced BC in Europe.

Methods:

We conducted a retrospective chart review of 355 postmenopausal women with HR⁺, HER2⁻ advanced BC who progressed on ≥ 1 line of HT (adjuvant or advanced) and completed ≥ 1 line of chemotherapy (advanced). Treatment choice was evaluated for each line of therapy.

Results:

Of 355 patients, 111 (31%) received first-line chemotherapy, whereas 218 (61%) and 26 (7%) switched from HT to chemotherapy in second and third line, respectively. More patients receiving first-line HT had bone metastases (73% vs 27% chemotherapy). Patients treated with first-line chemotherapy had more brain (12% vs 3% HT) or extensive liver (13% vs 6% HT) metastases. Subgroup analysis of 188 patients who received first-line HT and had *de novo* advanced BC or relapsed/recurrent disease more than 1 year after adjuvant therapy found that the majority (89%; $n = 167$) of these patients switched to chemotherapy in second line. However, among these 167 patients, 27% had no significant changes in metastases between first and second line. Among the 73% of patients who had significant changes in metastases, 20% had no brain metastases or extensive visceral disease.

Conclusions:

Our study suggests that the guideline-recommended use of multiple HT lines is open to interpretation and that optimal treatment for European postmenopausal women with HR⁺, HER2⁻ advanced BC who responded to HT may not be achieved.

Introduction

Guidelines for the number of lines of hormonal therapy (HT) that should be used and when to initiate chemotherapy in patients with hormone-receptor-positive (HR⁺) advanced breast cancer (BC) are not straightforward^{1–3}. This is due in part to the currently incomplete evidence base for the

recommendations, which can make the optimal treatment strategy open to interpretation. The European guidelines for the treatment of HR⁺, locally recurrent or metastatic BC recommend multiple, but an indeterminate number of, HT lines, and without defining HT response³. Chemotherapy is the recommended treatment when there is clear evidence of resistance to HT. The international consensus guidelines for advanced BC concur with the European guidelines regarding the use of HT as first choice and as a subsequent option following disease progression; however, no guidance is provided on the use of more than two lines of HT or criteria for switching to chemotherapy². The National Comprehensive Cancer Network guidelines recommend continuing HT regimens as long as clinical benefit was received from the previous HT regimen, without a clear definition of clinical benefit. In particular, the duration of stable disease that is clinically meaningful and implies hormone sensitivity is open to interpretation. Chemotherapy is recommended only if there was no clinical benefit from at least three consecutive HT regimens or there is a need for rapid disease control¹. In all three guidelines, chemotherapy is recommended when there is extensive and/or symptomatic visceral disease.

In addition to the guidelines for advanced BC, country-specific differences in access and use of various agents can influence the treatment regimen that a patient will receive⁴. For example, in Europe targeted therapies (e.g., bevacizumab and human epidermal growth factor receptor-2 [HER2] antagonists) are more likely to be used in France than in Germany and least likely to be used in the United Kingdom⁵. Furthermore, chemotherapy is used more frequently in Germany for advanced BC; in one study, only 48% of patients with HR⁺ BC were treated with endocrine therapy irrespective of the number of metastatic sites or number of organs involved⁶. Moreover, wide variation exists in terms of access to cancer therapies across European countries, with an emphasis on using generic agents first in countries such as Germany and most recently in Belgium.

Although evidence-based guidelines do provide some recommendations for optimal management of advanced HR⁺ BC, they may not always be followed or interpreted consistently by physicians. Understanding the reasons for differences between 'real-world' treatment decisions and guideline recommendations will enable further guideline clarification. Furthermore, lack of adherence to the guideline-recommended treatments may negatively affect quality of care in patients with BC^{2,7-9}.

This chart review is the first that evaluates actual physician-reported treatments from adjuvant therapy to completion of three lines of treatment in the advanced BC setting for the purpose of providing evidence of HT and chemotherapy treatment patterns in Europe and

assessing the results against guideline recommendations in order to highlight issues requiring further clarification.

Methods

Study objective

The objective of the study was to understand the clinical management and resource utilization of HR⁺, HER2-negative (HER2⁻) advanced BC, with the overall aim of depicting the treatment decisions as patients progressed from HT to chemotherapy in the advanced BC setting.

Study design

This was a retrospective chart review performed by physicians or healthcare providers in the areas of gynecology and medical or clinical oncology who treat advanced BC. The medical professionals were recruited from five European countries (Belgium, France, Germany, The Netherlands, and Sweden) and were selected based on years of clinical practice after residency or fellowship (≥ 5 and ≤ 35 years), proportion of time treating patients ($\geq 60\%$), and the number of patients with breast cancer for whom they were responsible for systemic treatment decisions in the year prior to the study (≥ 50 and ≤ 1000 patients). Data from the patient charts were collected via a questionnaire, and all patient charts remained anonymous. The study was compliant with both European and individual country regulations.

Chart selection criteria

Postmenopausal patients with HR⁺, HER2⁻ advanced BC diagnosed no earlier than 2008 were reviewed for eligibility. Advanced BC was defined as metastatic or locally advanced BC not amenable to curative treatment by surgery or radiotherapy. Patients (alive or deceased) with recurring or *de novo* disease had to have disease progression with at least one line of HT in the adjuvant or advanced BC setting (combinations with chemotherapy or targeted therapy were allowed) and had to have completed at least two cycles of at least one chemotherapy line in the advanced BC setting.

Data extraction

Data collected in the questionnaire consisted of patient demographics and disease characteristics/progression at the initiation of each treatment line, information on any/all metastases, and all comorbidities. Maintenance therapy was treated as a separate line of therapy rather than being included with the previous treatment. Treatment details requested for each line included agent,

dose, duration, and administration route. Data on targeted therapies (defined as any small-molecule or monoclonal antibody with a specific mechanism of action) used in combination with the primary therapy at each line were also requested. Targeted therapies frequently used to treat BC at the time of the chart review included bevacizumab, lapatinib, trastuzumab, and a range of investigational agents (e.g., poly ADP ribose polymerase, mammalian target of rapamycin, and tyrosine kinase inhibitors). In addition, data were collected on each patient's performance status. The reasons for switching to the next line of treatment were also collected.

Statistical analysis

The charts were stratified into three cohorts by key treatment algorithms based on sequence of HT and chemotherapy lines, and the information from the questionnaires was grouped accordingly. Descriptive statistics were used to summarize the physician and patient characteristics, treatment details, and decisions.

Results

Evidence base for chart review

Across the five European countries, 952 sites were approached for physician participation in the chart review; 94 qualified physicians contributed 399 eligible patient charts (3–9 charts per physician; Table 1). The physician locations were evenly distributed across Europe; however, slightly more charts came from France, and there was no representation from the Walloon region of Belgium. The majority of physicians reported a specialty of medical oncology (62%), whereas 23% reported clinical oncology and 15% reported gynecology. Most physicians reported that they treated 50–200 patients with BC in the year preceding this study, primarily at a teaching hospital (Figure 1). The majority of participating physicians have been in clinical practice for 5–10 years.

A total of 355 patient charts representing common treatment sequences were used in the analysis and placed into three cohorts: cohort A ($n = 218$) had HT first line,

chemotherapy second line, and any treatment third line; cohort B ($n = 26$) had HT first and second line with chemotherapy third line; and cohort C ($n = 111$) had chemotherapy first line with any treatment second and third line (Figure 2a). Forty-four patient charts were excluded from the analysis because they did not meet the key treatment algorithms established for the majority of patients who were placed into the three cohorts (36 patients had only one therapy line in advanced BC and 8 patients had HT for three treatment lines before chemotherapy). Overall, there were few differences across patient cohorts in terms of patient demographics and characteristics (Table 2). Notably, patients in cohort C were more likely to have a family history of breast and/or ovarian cancer and present with liver and/or brain metastases at advanced BC diagnosis. In addition, more patients in cohort B presented with extensive bone metastases.

Treatment patterns

In the first-line setting, 69% of all patients received HT (cohorts A and B). There were differences in BC histories and adjuvant therapies between patients who received first-line HT (cohorts A and B) and those who received first-line chemotherapy (cohort C). Of the patients who received HT first-line, cohort A had the highest proportion of patients with *de novo* advanced BC and cohort B had the highest proportion of patients with a later recurrence of disease (>1 year) after completing adjuvant therapy (Figure 2b). Patients in cohort C (chemotherapy as first line) had the highest proportion of disease recurrence during or within 1 year of completing adjuvant therapy. In addition, cohort C had the highest proportion of patients who also had received adjuvant chemotherapy (Figure 2c). Among all patients who received HT in the first-line setting ($n = 244$; cohorts A and B), the most commonly prescribed agent was tamoxifen (29%), followed by anastrozole (27%), letrozole (23%), exemestane (12%), and fulvestrant (9%). Among all patients who received chemotherapy in the first-line setting ($n = 111$; cohort C), the most commonly prescribed agents were docetaxel (23%) and paclitaxel (22%), followed by cyclophosphamide (19%), epirubicin (18%), and capecitabine (14%).

Table 1. Physicians and eligible charts reviewed by country.

Country	Physicians invited, n^a	Physicians who accessed survey, n	Physicians not eligible, n	Physicians participating, n	Gynecologists, % ^b	Charts, n
France	515	64	6	21	0	105
Germany	972	174	76	21	48	79
The Netherlands	774	70	22	19	0	68
Belgium (Flemish region)	71	36	8	17	24	84
Sweden	393	52	15	16	0	63

^aPhysicians invited via hospitals and clinics, except in France, where only specialist cancer centers were approached.

^bPercentage of participating physicians who were gynecologists.

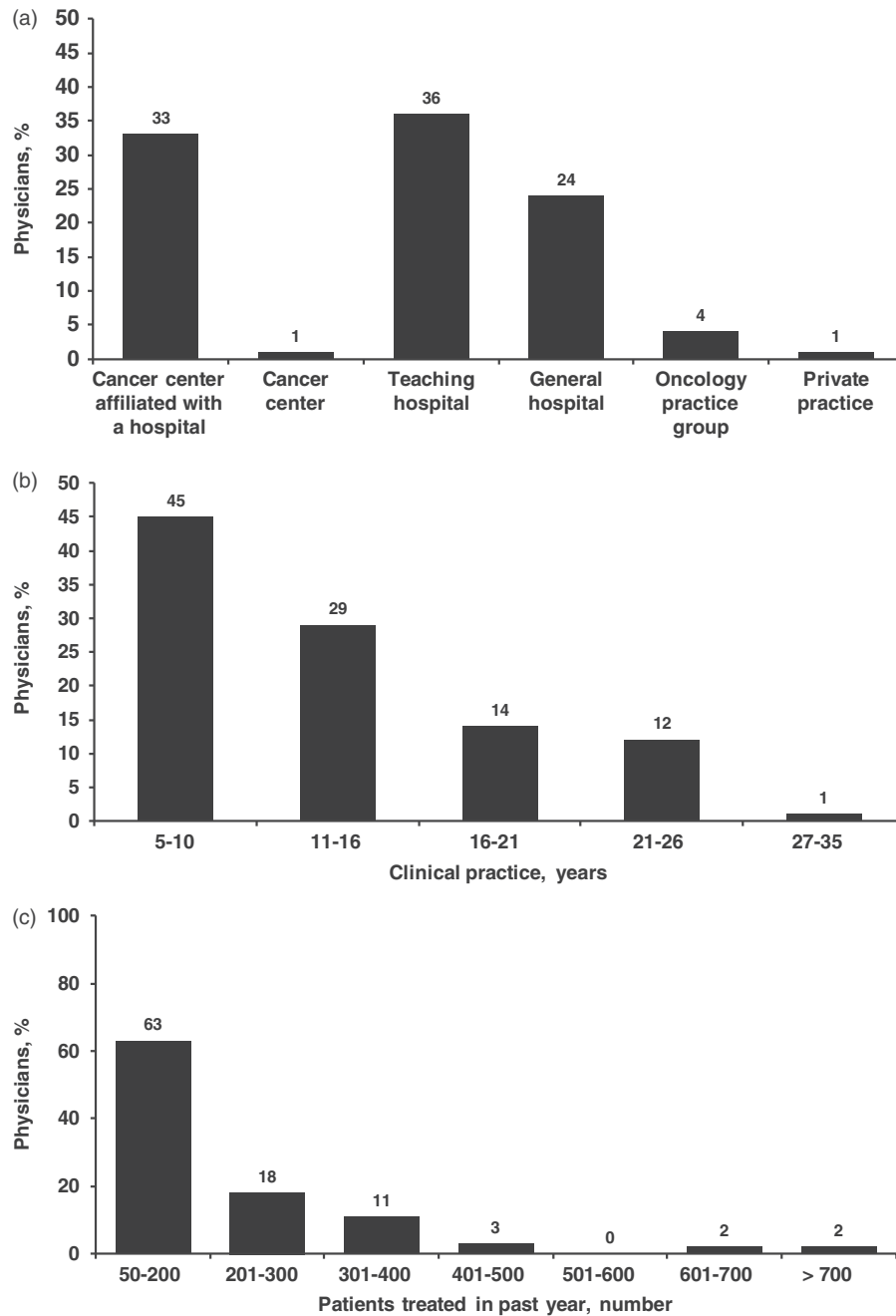


Figure 1. Overview of participating physicians by (a) type of medical institution, (b) years of clinical practice, and (c) number of patients with breast cancer treated in the past year.

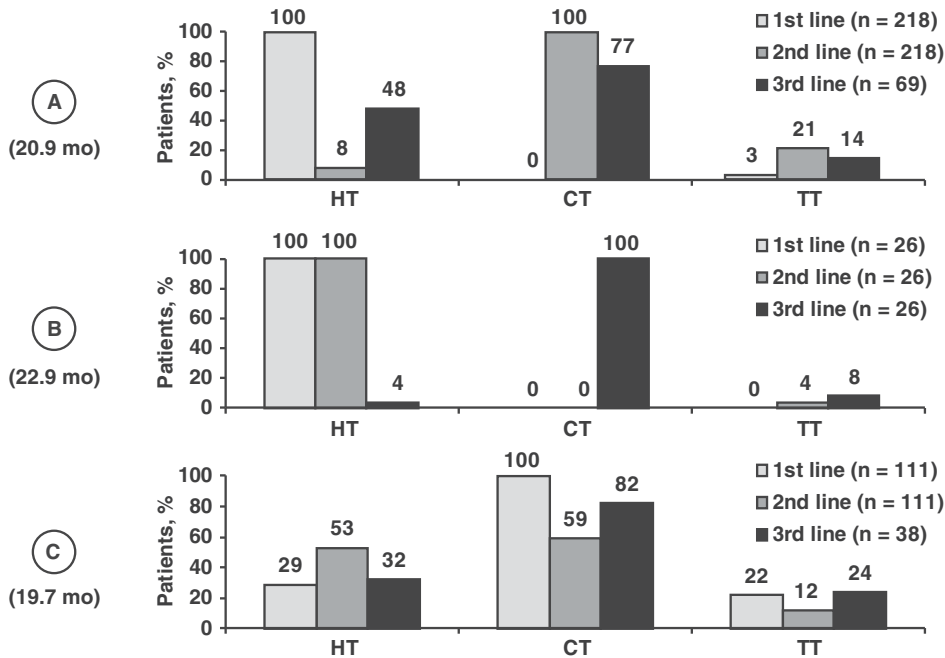
The most commonly prescribed targeted agent in the first-line setting ($n = 31$; cohorts A and C) was bevacizumab (65%), followed by trastuzumab (28%), lapatinib (2%), investigational agents (2%), and others (2%).

In the second-line setting, only 22% of all patients received HT. At the initiation of second-line treatment, 59% of all patients ($n = 212$) had a change in the extent or location of metastatic sites, mainly involving bone (63%), liver (54%), and lung (46%). Treatment choice changed in the second line compared with the first line; there was

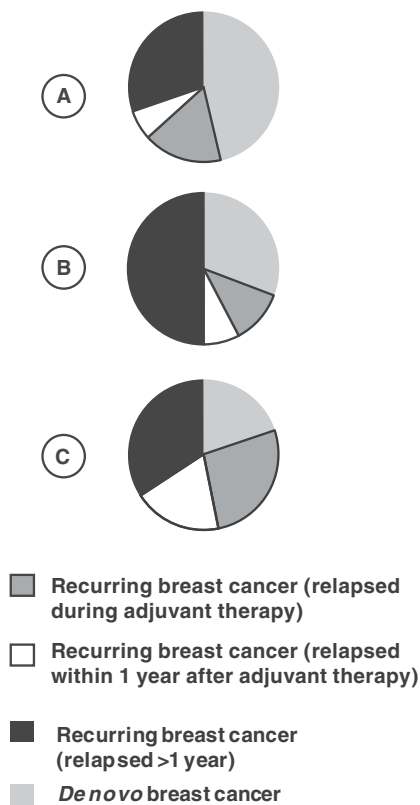
no preferred HT agent, and capecitabine (30%) became the most commonly prescribed chemotherapy agent. The distribution of targeted agents remained similar.

At the initiation of third-line treatment, 30% of all patients received HT (Figure 2a). The distribution of treatment was similar to that observed in the second-line setting, although 50% of all patients ($n = 71$) had a change in the extent or location of metastatic sites, mainly involving bone (70%), liver (63%), and lung (51%). The treatment pattern for HT agents changed from second to third line,

(a) Cohort
(Average duration of Tx;
1st - 3rd line)



(b)



(c)

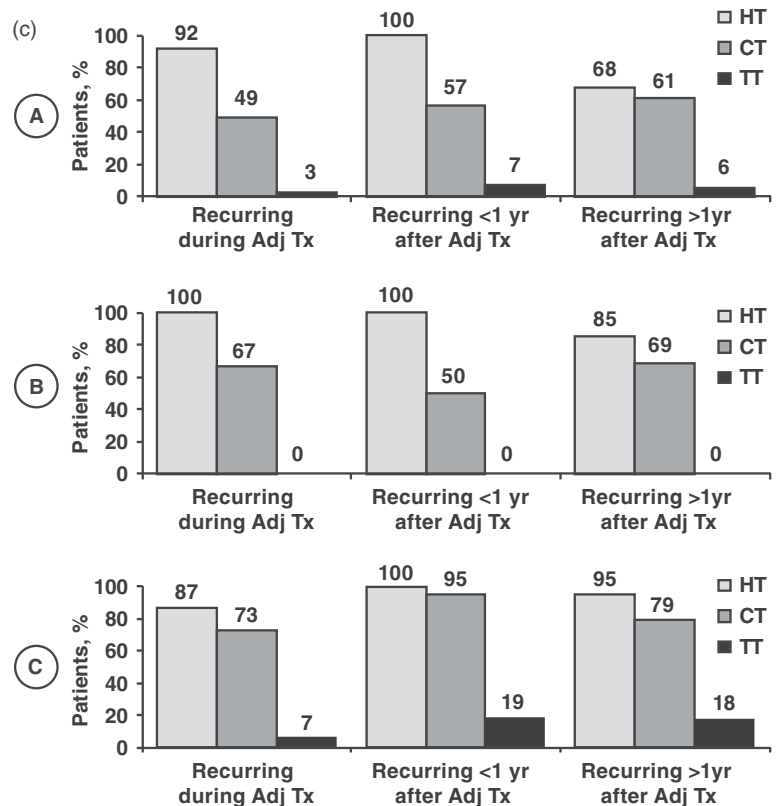


Figure 2. Patient cohorts by (a) treatment received by line in advanced breast cancer setting, (b) breast cancer history, and (c) adjuvant therapies received. A subset of patients with recurrent breast cancer did not receive pharmacologic intervention in the adjuvant setting. Adj, adjuvant; CT, chemotherapy; HT, hormonal therapy; TT, targeted therapy; Tx, therapy.

Table 2. Patient demographics and disease characteristics at advanced BC diagnosis.

	Cohort A ^a (n=218)	Cohort B ^b (n=26)	Cohort C ^c (n=111)	Overall (n=355)
Median age, years	64	61	61	63
Family history, breast/ovarian cancer, %	16	12	26	19
ECOG performance status, %				
0–1	77	100	85	81
2–4	20	0	15	17
Unknown	3	0	0	2
AJCC stage grouping, %				
IIIA	19	15	14	17
IIIB	10	0	14	11
IIIC	4	0	8	5
IV	67	85	63	67
Strong PgR ⁺ status, % ^d	71	73	62	68
Tumor proliferation, % ^e				
Ki-67 status <20%	12	8	18	14
Ki-67 status unknown	58	73	36	52
Tumor grade 3, %	46	42	48	46
Metastatic site, %				
Brain	3	0	12	6
Lung	33	23	32	32
Liver	28	12	47	32
Bone	54	85	54	56

^aCohort A had hormonal therapy first line, chemotherapy second line, and any treatment third line.

^bCohort B had hormonal therapy first and second line with chemotherapy third line.

^cCohort C had chemotherapy first line with any treatment second and third line.

^dMay reflect baseline characteristics before advanced breast cancer diagnosis where biopsy was not conducted at advanced breast cancer diagnosis. Strength of PgR⁺ status was defined by physician indication of strongly positive or weakly positive.

^eKi-67 and grade 3 categories are not mutually exclusive.

AJCC, American Joint Committee on Cancer; BC, breast cancer; ECOG, Eastern Cooperative Oncology Group; PgR⁺, progesterone-receptor-positive.

with letrozole (27%), exemestane (25%), and fulvestrant (23%) preferred over tamoxifen (15%) and anastrozole (13%). The patterns for chemotherapy and targeted agents remained similar to those at second line. Patient performance status deteriorated with increasing lines of therapy, but was not strongly correlated with the transition from HT to chemotherapy (Figure 3).

Treatment switch rationale

For patients who remained on HT for second-line treatment, physicians reported the absence of life-threatening metastases and slow speed of disease progression as the main reasons for this treatment choice (Figure 4a). Physicians reported rapid disease progression as the main reason for switching from HT to chemotherapy for second-line treatment (Figure 4b). Additionally, among patients switching from chemotherapy to HT for later lines of treatment, patients' requirement for a break from chemotherapy was an increasingly important reason for the switch.

Differences between guideline-recommended and reported treatments

In general, the majority of patients who received HT and chemotherapy as their first-line treatment were

appropriately treated according to international guidelines. A few patients who received HT first-line had disease recurrence and extensive liver and/or brain metastases (n=5) during or within 1 year of completing adjuvant treatments and were, therefore, eligible for first-line chemotherapy. Only four patients who received chemotherapy first line had limited bone-only metastases and BC recurrence more than 1 year after completing adjuvant therapy and thus were eligible for first-line HT.

A larger subgroup of patients who were eligible for and received HT as first-line treatment according to international guidelines (*de novo* advanced BC or advanced BC recurrence more than 1 year after completing adjuvant therapy) were also analyzed (n=188). Most (89%; n=167) of these patients were switched to chemotherapy in second line. However, 27% (n=45) had no significant changes in metastases between first- and second-line treatment, and the mean duration of first-line therapy was 9.5 months. Furthermore, among the 122 patients (73%) who had significant changes in metastases, 34 had no brain metastases or extensive visceral disease, and mean duration of first-line therapy was 8.7 months. All together, there were 79 patients who guidelines would recommend remain on HT for second-line treatment (based on the duration of clinical benefit in first line and absence of visceral disease), but who actually received chemotherapy

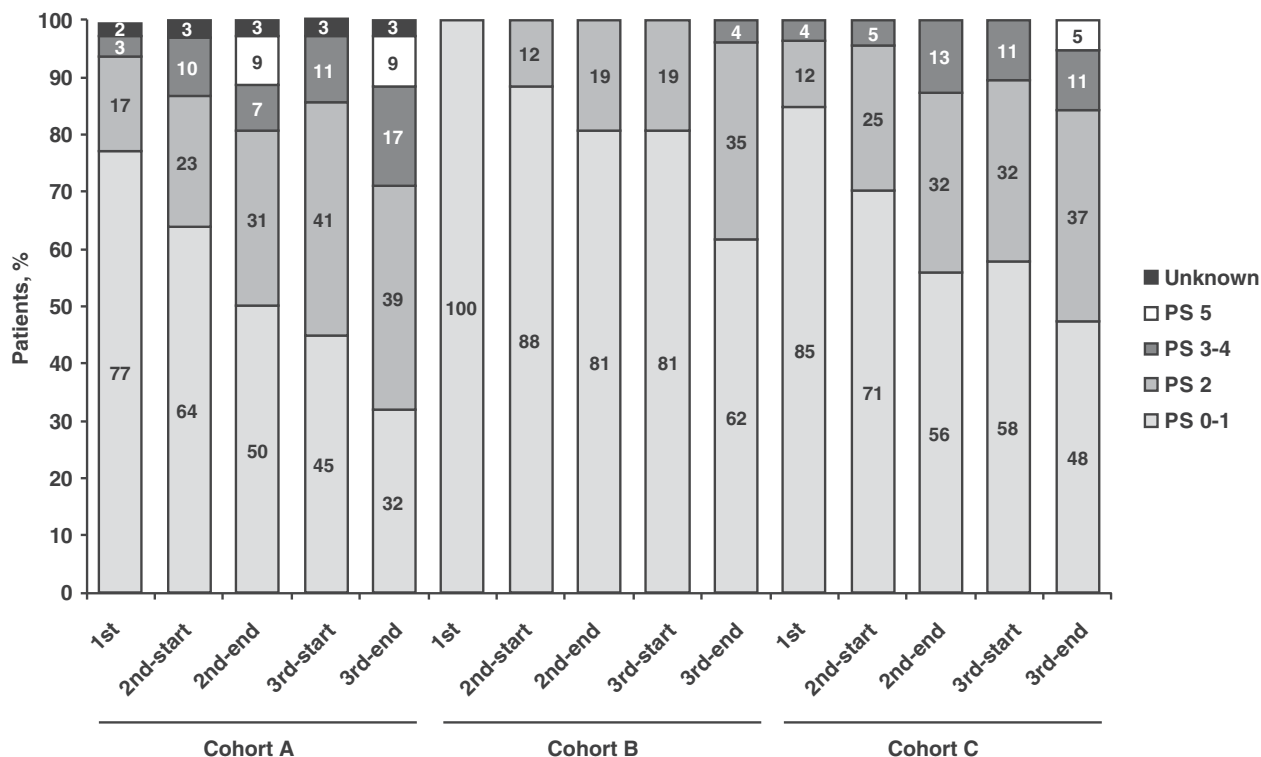


Figure 3. Change in performance status at the start and end of each treatment line by cohort. Performance status (PS) was reported as Eastern Cooperative Oncology Group 0–5.

in second line. These 79 patients represent 22% of our total sample for this chart review (n = 355) (Table 3).

Discussion

Guidance for when to use HT versus chemotherapy and when to switch from HT to chemotherapy is not always clear and consistent in the treatment recommendations for advanced HR⁺ HER2⁻ BC¹⁻³. For example, there are variations in the number of HT lines that can be used before switching to chemotherapy, the duration of HT before disease progression (i.e., the duration of disease control during HT) that constitutes a clinical benefit, and the definition of disease progression/stabilization versus response. In this analysis, the reporting physicians represented the typical treating healthcare providers in each country, with sufficient clinical experience (based on years in practice and number of patients treated) to interpret the guidelines and make a treatment choice. In general, the physician’s choice of initial first-line HT or chemotherapy was consistent with guideline recommendations; only a small proportion of patients eligible for first-line chemotherapy received first-line HT and vice versa. Although the inclusion criteria for this study required at least one line of chemotherapy, the overall proportion of patients receiving first-line chemotherapy

appears high (>30%), especially considering the toxicities associated with chemotherapy and the guidelines statement that visceral metastases are not a contraindication for HT^{1,2}. A recent review of clinical studies in the advanced BC setting showed that the average median overall survival was 31.1 months with first-line HT and 20.7 months in trials assessing first-line chemotherapy, although patient characteristics were not analyzed to ascertain the degree of disease burden in these studies¹⁰. Furthermore, compared with HT, the use of chemotherapy is associated with increases in direct costs and resource utilization such as monitoring tests, treatments to manage adverse events, and hospitalizations¹¹.

Physician use of HT versus chemotherapy in second-line treatment was not as consistent with guideline recommendations. Although the physicians frequently cited rapid disease progression as the main reason for switching from HT to chemotherapy, the data for the patient characteristics did not appear to corroborate this decision. Approximately 50% of the patients in cohort A who received chemotherapy second line had extensive visceral metastases or other clinical indicators consistent with rapid disease progression (e.g., short duration of first-line therapy or high tumor proliferation status).

The drivers of inconsistency between guideline-recommended and actual use of second-line chemotherapy in this chart review probably included lack of clarity in

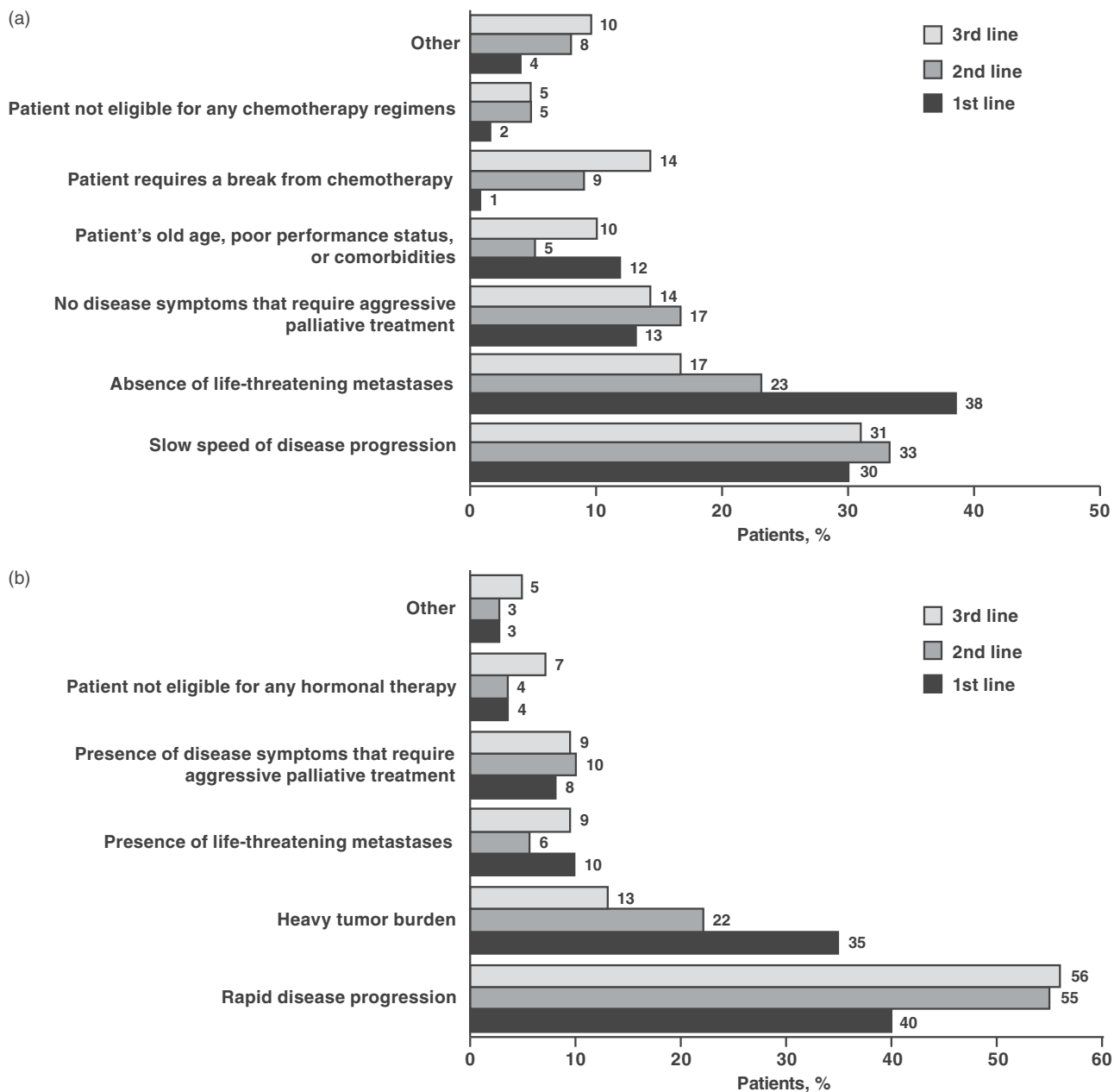


Figure 4. Physician-reported reasons for treatment choice of (a) hormonal therapy over chemotherapy and (b) chemotherapy over hormonal therapy at each line of treatment. (Panel a): Other reasons include patient desire, not hormone refractory, radiotherapy, consolidation, and regression for as long as possible after recent chemotherapy. (Panel b): Other reasons include patient desire, new metastases or progression during hormonal therapy, triple-negative biopsy or hormone-negative metastasis, maintenance chemotherapy, and can be combined with targeted therapy.

definitions of HT response and rate of disease progression in guideline recommendations. Possible contributors to these discrepancies are a lack of clinical evidence and inconsistencies in the available evidence. For example, clinical trials contributing to treatment guidelines do not provide consistent definitions for endpoints regarding disease progression and recurrence^{12,13}. The time point at which progression and/or recurrence is detected after adjuvant therapy to qualify as hormone-refractory disease

differs among clinical trials, with some trials further delineating the time into primary and secondary resistance¹⁴⁻¹⁶. In addition, one study that examined adherence to BC guidelines over 3 years in a hospital in France found that nonadherence to treatment recommendations was more likely with uncommon patient clinical profiles and in areas where clinical evidence was lacking^{17,18}. Specifically, if physicians considered the guideline recommendation to be based on too little evidence or the

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Table 3. Patient demographics and disease characteristics at advanced BC diagnosis by hormonal treatment eligibility in first-line treatment.

	HT refractory ^a		HT eligible ^b	
	Cohort A ^c (n = 48)	Cohort C ^d (n = 47)	Cohort A ^c (n = 167)	Cohort B ^e (n = 21)
Median age, years	62	59	65	61
AJCC stage grouping, %				
IIIA	17	15	19	14
IIIB	10	9	10	0
IIIC	10	13	2	0
IV	63	64	69	86
Tumor proliferation, % ^f				
Ki-67 status <20%	6	9	14	10
Ki-67 status unknown	60	43	56	71
Tumor grade 3, %	60	49	41	33
Metastatic site, %				
Brain	10	15	1	0
Lung	38	30	32	19
Liver	25	45	28	10
Bone	58	57	54	81

^aHT-refractory disease was defined as relapsed/recurrent disease during adjuvant therapy or within 1 year after adjuvant therapy.

^bHT-eligible disease was defined as *de novo* advanced breast cancer or relapsed/recurrent disease >1 year after adjuvant therapy.

^cCohort A had hormonal therapy first line, chemotherapy second line, and any treatment third line.

^dCohort B had hormonal therapy first and second line with chemotherapy third line.

^eCohort C had chemotherapy first line with any treatment second and third line.

^fKi-67 and grade 3 categories are not mutually exclusive.

AJCC, American Joint Committee on Cancer; BC, breast cancer; HT, hormonal therapy.

evidence showed a doubtful patient outcome, physicians chose treatment options based on their clinical department procedures.

Another emerging factor in the interpretation of guidelines is the use of targeted therapies. In this study, targeted therapies were used more with chemotherapy than with HT. However, recent evidence suggests that multiple lines of HT with different endocrine agents and combinations with newer targeted agents provide clinical benefit in appropriate patients^{14,19}. In the current guidelines, anti-HER2 agents and the antiangiogenic agent bevacizumab are generally considered targeted therapies; the newer targeted agents are considered additional therapies to overcome endocrine resistance^{1,3}. The use of these newer targeted agents was too sparse to assess in our study and will need to be reviewed for appropriate initiation in future analyses.

The limitations of our study primarily stem from the limitations for a retrospective chart review. In reviewing chart information, there are limitations to the amount of available data. For example, missing data that could affect treatment decisions, such as reported symptoms or updated HER2 status, could bias the perception of treatment patterns. For example, although the inclusion criteria stated that only patients with HER2⁻ disease were eligible, a small proportion of patients received trastuzumab and lapatinib. These patients could have had confirmed HER2⁻ primary disease, and HER2-targeted therapies were subsequently used to treat suspected HER2⁺ metastatic disease or because of limited treatment options. In addition, accurate information on treatment decisions

made in the past may be incorrectly recalled. Also, information with which the treating physician is not familiar (e.g., agents used in the adjuvant setting) may be limited. This study tried to mitigate these concerns by having the treating physician complete the questionnaire using relatively recent patient charts.

Conclusion

Although treatment patterns for advanced BC in Europe were generally consistent with guideline recommendations, important discrepancies were identified regarding definitions of disease progression and HT response in the treatment of European postmenopausal women with HR⁺ HER2⁻ advanced BC who responded to HT. Resolving these issues could improve disease management. Further work is needed to standardize the designation of hormone-refractory disease, which would clarify when to switch from HT to chemotherapy.

Transparency

Declaration of funding

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Declaration of financial/other relationships

F.A. has participated in advisory boards and speaker bureau for, and has received research funding from Novartis Pharmaceuticals Corporation. P.N. has disclosed that he has no significant

relationships with or financial interests in any commercial companies related to this study or article. N.M. has received consultancy fees from Novartis Pharmaceuticals Corporation. J.Z. is a Novartis employee and shareholder. J.-F.B. has received remuneration from and is a shareholder of Novartis Pharmaceuticals Corporation. R.D. has received consultancy fees from Novartis Pharmaceuticals Corporation. G.B. is a Novartis employee and shareholder. S.S. is a Novartis employee and shareholder. G.J. has received consultancy fees and research funding from Novartis Pharmaceuticals Corporation.

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