Quality of Life under Capecitabine (Xeloda®) in Patients with Metastatic Breast Cancer: Data from a German Non-Interventional Surveillance Study

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Summary

Aim: This non-interventional surveillance study (NIS) collected data on the quality of life (QoL) of patients treated with capecitabine as mono- or combination chemotherapy in an outpatient setting. **Methods:** Capecitabine was administered orally for 14 days of each 21-day cycle. The main parameters of interest were QoL, compliance, patient and physician satisfaction, handling of hand-foot syndrome (HFS), and efficacy. The statistics were descriptive; some differences were compared using confidence intervals (CIs). **Results:** 735 patients from 161 centers received at least 1 dose of capecitabine. The median duration of observation was 5.5 months overall. The QoL global score was 53% (mean from the entire study population at all times), without any correlation to HFS. The overall response rate (ORR) was 35.1%, and the disease control rate (DCR) 64.4%. The median progression-free survival (PFS) was overall 6.81 months (95% CI 6.32–7.63 months) and it was significantly higher in patients with HFS (8.4 months, 95% CI 7.5–9.2 months,

hazard ratio (HR) 0.60; $p < 0.0001$). The safety and tolerability of capecitabine were considered acceptable. The HFS incidence (all grades) was 27.1%. **Conclusions:** Capecitabine had a favorable risk-benefit relation in outpatient therapy. The QoL remained stable over the course of the investigation, indicating good compliance. HFS was a strong predictor of longer PFS and had no negative impact on the global QoL.

Introduction

Breast cancer is the most common tumor in women. Worldwide, it accounts for more than 27% of all cancers and for about 15% of the cancer deaths in women (World Cancer Report 2014, www.iarc.fr).

In patients with metastases at primary diagnosis or recurrence following successful initial treatment, capecitabine (Xeloda®, Roche Pharma AG, Grenzach-Wyhlen, Germany) can be applied as a chemotherapeutic agent. The drug reduces DNA synthesis via inhibiting the thymidylate synthase and inhibits the synthesis of RNA particularly in tumor cells by blocking nucleoside analogues [1]. Following absorption by

the mucous membrane of the small intestine, the prodrug is enzymatically converted to its pharmacologically active form, 5-fluorouracil. This activation follows a pathway of 3 enzymatic steps and 2 intermediary metabolites which also show pharmacological activity. In tumor cells with high proliferative activity, the concentration of the key enzyme for this transformation, thymidine phosphorylase, is essentially higher than in non-malignant tissues, supporting a specific antitumor activity of capecitabine. Even in tumor cells with insufficient blood supply, the concentrations of 5-fluorouracil have been reported to be more than 100-fold higher than in the blood [2]. As a result, capecitabine has the potential to stop the proliferation of tumor cells in association with lower toxicity compared to other chemotherapies. In contrast to many other medications for cancer chemotherapy, capecitabine can be administered orally, which makes it a convenient choice for self-administration – a feature that especially suits women with breast cancer who want to maintain their independence.

According to data from various clinical trials, capecitabine alone or in combination with docetaxel is one of the most effective drugs in the treatment of metastatic breast cancer [3–6]. However, data from clinical studies cannot necessarily be transferred to conditions of everyday use. Discrepancies could be due to different compliance in non-selective patient collectives. In particular, subgroups such as elderly patients might be involved. Parameters like visual impairment, worries about potential adverse effects, and excessive demands of medical consultations may lead to inadequate compliance and slow or overanxious reactions to side effects. Subsequently, the patients' satisfaction as well as the therapeutic effectiveness could be impaired. Knowledge gained under conditions of clinical routine use could be essential for the creation of an optimal therapeutic handling of the drug. The transferability of study results into doctors' and patients' daily routines, and the impact on 'real-world patients' and their lives, should be evaluated and used to improve and fine-tune therapeutic administration schedules.

Recently, besides measurable tumor parameters, the subjective perception regarding quality of life (QoL) has become an important therapeutic objective. This is true both in the early stages when women seek to participate in everyday life and in the metastatic setting. Many recent major trials have employed QoL as secondary endpoint. In this regard, the orally available and specific chemotherapeutic agent capecitabine offers several gains for the patients. The medication may be applied at home, saving venous punctures and medical consultations, and thus potential risks, time, and expenses for the patients. In addition, the patients can assume an active role in their own therapy, an important contributor for compliance and for emotional perseverance. Outside clinical settings, compliance and QoL strongly interact with each other, influenced by both the efficacy and the safety of the drug. It is a cause of concern how patients will experience and react to side effects and how adverse drug effects will influence their compliance, the QoL, and finally their outcomes.

A very common and sometimes dose-limiting side effect of capecitabine is hand-foot syndrome (HFS; palmar plantar erythrodysesthesia). This painful erythematous skin lesion is frequently located at the inner hand and at the soles of the feet. HFS is mostly associated with local pressure sensitivity and paresthesia, up to blistering and skin detachments. Several investigators already stressed a significant correlation between HFS and some efficacy markers of capecitabine [7], suggesting that HFS may be a positive indicator of cellular activity.

So far, no data have been collected on the impact of HFS on the QoL of cancer patients under treatment with capecitabine. It is the aim of this non-interventional surveillance study (NIS) to collect data concerning the treatment schedules, the QoL, and the outcomes of metastatic breast cancer patients treated with capecitabine, in order to target an ideal application in everyday use.

Methods

Study Design

The study was a multicenter, post-marketing NIS assessing the QoL in patients with metastatic human epidermal growth factor receptor 2 (HER2)-negative or -positive breast cancer treated with capecitabine. The study was not randomized, not controlled, and not blinded.

The purpose of this investigation was to document the QoL under capecitabine treatment as a part of routine breast cancer treatment in Germany. The implementation of this NIS did not influence the physicians' decisions regarding diagnostics, therapy, or frequency of medical examinations during and after the treatment. The investigator population included oncologists and gynecologists in clinics and outpatient clinics, and office-based physicians specialized in oncology. Since there is still a need for further evidence on objective and subjective parameters like course of therapy, expectations, information, and treatment-relevant control options by the physician, the QoL documentation was linked to further interrogations.

Ethics committee approvals were obtained before enrolment of any patients in the study, which was performed in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines. The investigation was conducted according to the recommendations of the Bundesinstitut für Arzneimittel und Medizinprodukte (BfArM; Bonn, Germany) as well as the Paul-Ehrlich-Institut (PEI; Langen, Germany) and the Verband der forschenden Arzneimittelhersteller (VfA; Berlin, Germany). Written informed consent was obtained from all patients before study entry. The NIS was sponsored by the manufacturer of capecitabine, Roche Pharma AG.

Patients

HER2-negative or -positive patients with metastatic breast cancer aged ≥ 18 years were enrolled. Furthermore, the participants had to be pre- or postmenopausal women with first- or further line locally advanced recurrent or metastatic breast cancer, eligible for a mono- or polychemotherapy with capecitabine by the physician's decision.

Key exclusion criteria were contraindications for capecitabine according to the summary of product characteristics.

Treatment

Capecitabine is an approved medication for oral treatment of metastatic breast cancer. Administration was performed in accordance with the summary of product characteristics. Recommended dosing regimens

Table 1. Patient questionnaires

Questionnaire	Number of questions	Baseline	Cycle											
			1	2	3	4	5	6	7	8	9	10	11	12
Compliance 1	2		x	x	x	x	x	x	x	x	x	x	x	x
Compliance 2	1							x						x
QLQ-C30 + HFS ^a	31	x			x			x			x			x
Patient satisfaction with therapy information	16	x												

^aAdditional item in the QLQ-C30 questionnaire concerning HFS.

for mono- and combination therapy were 1,250 mg/m² twice daily for the duration of 14 days, followed by a therapy break of 7 days. The maximum treatment duration per patient was 9 months exclusive of the follow-up period. Combination partners for capecitabine were not specified, but left to the discretion of the treating physician, provided the use was in accordance with the regulatory specifications.

During treatment, all patients of childbearing potential had been obliged to use reliable and effective forms of contraception. In case of pregnancy, data concerning the course and outcome with respect to the development of the fetus as well as any possible cause-effect relationship to the treatment were to be collected.

Assessments

Questions of particular importance were the overall and domain-related QoL, compliance with capecitabine treatment, patient satisfaction with the capecitabine therapy, physician satisfaction with the capecitabine therapy, knowledge and satisfaction of the patients with their patient-physician communication and care, criteria that determined the therapy choice for capecitabine, handling of HFS if this event occurred, response and time-based efficacy parameters of capecitabine mono- or combination chemotherapy, demographic characteristics, and the medical history of the patient.

General information concerning the capecitabine therapy included data on therapy choice, possible combination treatment, supportive therapy, palliative radiotherapy, therapy evaluation from a medical perspective, therapeutic success, tumor response, and progression-free survival (PFS).

The assessment by the patients was performed using established and validated questionnaires on QoL (European Organisation for Research and Treatment of Cancer Quality-of-Life Questionnaire (EORTC QLQ)-C30 subscales), HFS, compliance, and contentment with therapy information, which were sent to the patients at baseline and at the treatment cycles 3, 6, 9 and 12 (table 1). The QoL questionnaire consisted of 30 questions on the general QoL (global scale), 5 functional scales (physical, role, emotional, cognitive, social), 3 symptom scales (fatigue, nausea/vomiting, pain), and 6 single items (dyspnea, sleep disturbances, anorexia, constipation, diarrhea, financial difficulties). Additional surveys of compliance were made at each cycle. In order to increase the number of returns, the respective questionnaires were sent directly to the patients at the scheduled dates. The completed electronic questionnaires were automatically checked for completeness and plausibility. In addition, documentation of adverse events was audited manually. Participating physicians were obliged to provide all background information pertaining to their records on request.

In addition, in order to substantiate the patient-reported outcomes, data on adverse events were collected by the investigator in the patient case report form (CRF). For each event, start and end date, severity, causality assessment, and outcome were recorded. Likewise, objective medical data including tumor status, dates of progression, and subjective decisions (choice of therapy, satisfaction, etc.) were recorded by the investigator. Data from the completed questionnaires were submitted anonymously

Table 2. Patient distribution

Number of patients enrolled	Number of centers, n (%)
> 30	1 (0.6)
20–30	2 (1.2)
10–20	16 (9.9)
< 10	142 (88.2)

mously by a password-protected routine. Identification was performed via the patient's date of birth, the questionnaire number, and the identification number of the respective center.

Statistical Analysis

Comparisons between monotherapy and combination therapy concerning the number of treatment sequences, cycles without capecitabine application, dosage modifications, unexpected interruptions of therapy, and mean dose density were performed using only descriptive statistics. Reasons for dosage modifications, missing applications, and therapy intermissions were presented as absolute and relative frequencies. Differences in QoL scales between mono- and combination therapy were assessed as mean differences with respective confidence intervals (CIs). Detailed considerations were made by ad hoc analyses. For the evaluation of effects on PFS, a Cox proportional regression model was used. Combination drug, therapy line, and occurrence of HFS were included as covariates. Drug-related adverse events were summarized and displayed after Medical Dictionary for Regulatory Activities (MedDRA) coding. 3 descriptive interim data analyses were performed in addition to the final statistical analysis.

QLQ-C30 subscales were evaluated as specified by the EORTC handbook [8]. Subscales were exploitable if at least 50% of the questions were answered. Values of subscales and the additional question concerning HFS were scaled in a range from 0 to 100.

Results were presented for administration of capecitabine as monotherapy and the main combination therapies (capecitabine with bevacizumab, lapatinib, vinorelbine, or trastuzumab).

Results

It was intended to assess 750 patients in this NIS. 756 patients were registered, of which 754 started documentation and 735 received at least 1 dose of capecitabine. The study was conducted at 161 centers. The majority of centers (142/161; 88%) contributed less than 10 patients (table 2). 3 centers enrolled more than 20 patients.

The mean age of the patients at their primary diagnosis of breast cancer was 55 years, and the average time between pri-

mary diagnosis and the start of capecitabine treatment within this interventional study was 7 years. On entering the study, patients who received capecitabine as a monotherapy were, on average, about 4 years older than patients with combination therapy (64.1 vs. 60.1 years; $p < 0.0001$). Therefore, the proportion of patients of < 65 years was higher in the combination therapy group than for monotherapy (63.2% vs. 47.7%). In both treatment groups, more than 90% of the patients were pretreated. 107 had received a neoadjuvant and 296 an adjuvant therapy. The median duration of treatment with antibodies, mostly as maintenance therapy, amounted to 3.8 months for the neoadjuvant and 11.2 months for the adjuvant therapeutic approach, respectively. A pretreatment with taxanes or anthracyclines was documented for 60.4% in the monotherapy group and for 55.4% in the combination group. About half of the patients were additionally treated with hormones while 70.9% had received radiation therapy.

In this investigation, the decision concerning the therapeutic regimen was made by resident oncologists or tumor boards/centers for breast cancer. General condition, HER2 status, and tolerability were the most important criteria reported in both groups for choosing capecitabine. Age was a

secondary factor. In contrast to the tumor boards, resident oncologists favored combination therapy over monotherapy (40% vs. 30%, respectively).

At the beginning of the capecitabine therapy, in this study, the vast majority of the patients had an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1. 37.1% of the patients were status 0, corresponding to an unlimited physical activity; 45.6% were status 1, i.e. with moderately restricted physical and working ability.

Of 735 patients who received at least 1 dose of capecitabine (table 3), 346 received the drug as monotherapy and 389 in combination. The distribution of treatment lines and combination partners is shown in table 4.

The median overall observation period during the study amounted to 5.5 months, ranging between 0.0 and 19.1 months. Although no statistical comparisons were made, combination therapy with trastuzumab provided the longest mean and median observation times (6.5 and 6.7 months, respectively); with 5.3 months, capecitabine monotherapy and combinations with bevacizumab and vinorelbine appeared somewhat shorter.

Efficacy

The overall response rate (ORR) was 35.1% and the disease control rate (DCR) was 64.4%. 31 patients (4.2%) achieved a complete remission (best response); 14 of these belonged to the monotherapy group and 17 received a combination therapy. The response rates and DCRs were almost identical in both groups (table 5).

At the end of the main observation period of 9 months, 389 patients (52.9%) had progressed. 346 patients (47.2%) had been censored. The median PFS was determined to be 6.8 months (95% CI 6.3–7.6 months). Although the populations are different and should thus not be compared directly to each other, the results were very similar for the monotherapy (6.5 months; 95% CI 5.7–7.9 months) and the combination therapy group (7.0 months; 95% CI 6.5–8.3 months). A progression of the disease was attributable to distant metastases. The highest incidence rates were found for bones (55.1%), liver (41.1%), and lung (30.2%). In 28.8% of the patients, a local recurrence was diagnosed.

There were too few events to perform an analysis of overall survival.

Table 3. Patient disposition

Population	n (%)
Patients	
With registration by fax	765 (100.0)
With documentation in eCRF	754 (99.6)
Who received at least 1 dose of capecitabine (ITT)	735 (96.1)
Observed over 12 cycles	178 (23.3)
Assessment population	
ITT	735 (100.0)
QoL data available	628 (85.4)
Reasons for preterm study termination (ITT)	
Death	61 (8.3)
Adverse events	91 (12.3)
Lack of effectiveness	267 (36.3)
Compliance	5 (0.7)
Lost to follow-up	5 (0.7)
Complete or partial response	33 (4.5)
Patient's desire, physician's decision, etc.	116 (15.8)
Unknown	15 (2.0)

Table 4. Treatment lines and combination regimens

	1st line, N (%)	2nd line, N (%)	3rd line, N (%)	> 3rd line, N (%)	Total, N (%)
Patients total	306 (100.0)	215 (100.0)	114 (100.0)	99 (100.0)	735 (100.0)
Monotherapy	127 (41.5)	108 (50.2)	59 (51.8)	51 (51.5)	346 (47.1)
Combination therapy	179 (58.5)	107 (49.8)	55 (48.2)	48 (48.5)	389 (52.9)
Combination ^a with					
Bevacizumab	79 (44.1)	30 (28.0)	9 (16.4)	10 (20.8)	128 (17.4)
Lapatinib	23 (12.8)	35 (32.7)	28 (50.9)	17 (35.4)	103 (14.0)
Trastuzumab	40 (22.3)	21 (19.6)	8 (14.5)	9 (18.8)	78 (10.6)
Vinorelbine	46 (25.7)	29 (27.1)	12 (21.8)	10 (20.8)	97 (13.2)

^aSome patients received combinations with more than 1 drug.

Table 5. Best response

	Monotherapy		Combination therapy		Overall	
	n	%	n	%	n	%
Response	346	100.0	389	100.0	735	100.0
Complete remission	14	4.0	17	4.4	31	4.2
Partial response	85	24.6	142	36.5	227	30.9
Stable disease	112	32.4	103	26.5	215	29.3
Progression	82	23.7	87	22.4	169	23.0
Response rate						
Overall response rate	99	28.6	159	40.9	258	35.1
Disease control rate	211	61.0	262	67.4	473	64.4

Table 6. Duration of HFS

Therapy	N ^a	Mean (SD), days	Range, days	Median, days
Overall	49	52.7 (49.8)	2.0–202.0	35.0
Monotherapy	19	54.3 (57.1)	2.0–202.0	28.0
Combination therapy	30	51.7 (45.6)	6.0–166.0	39.0
Bevacizumab	8	54.8 (56.3)	6.0–166.0	34.5
Lapatinib	10	32.8 (30.9)	6.0–92.0	17.0
Vinorelbine	3	59.0 (44.2)	22.0–108.0	47.0
Trastuzumab	5	39.6 (39.2)	7.0–106.0	22.0

^aPatients with finished treatment of HFS.

HFS = Hand-foot-syndrome, SD = standard deviation.

Safety

The safety of capecitabine therapy was determined by recording (serious) adverse events and via analysis of relevant laboratory parameters. Adverse events were documented for 71.8% (N = 528) of the patients. The most common events were HFS (38.9%), diarrhea (20.3%), emesis (9.4%), and fatigue (7.5%). 147 patients (20%) had serious events.

Overall, in 91 of 765 registered patients (11.9%) adverse events led to treatment discontinuation. The main events that led to discontinuation of the therapy were skin reactions including HFS, erythema and blistering (2.5%; N = 19), emesis (1.9%; N = 14), and diarrhea (1.8%; N = 13). Most instances of HFS were mild, although HFS was the most frequent adverse event needing treatment (N = 107; 19.1%). There were no obvious differences between monotherapy and combinations.

60 patients died during therapy, 46 of them directly related to their tumor disease. The mortality was 8.4% for the monotherapy group and 8.0% for combination therapy. No correlation to the applied medications – mono- or combination therapy of capecitabine – could be detected. Evaluation of the occurring relevant or abnormal hematologic parameters revealed just minimal differences between the two therapy groups. No relevant additional safety issues were detected.

The assessment concerning QoL (QLQ-C30 subscales), HFS, compliance, and contentment with information on therapy was performed by questionnaires. From 628 out of 735 patients of the intention-to-treat (ITT) population (85%) at least 1 completed questionnaire was available at the end of

the study. Despite this very good response rate and compliance, in the 12th cycle, too few forms were returned to compare the treatment groups. 140 questionnaires would have been necessary for evaluation, but just 89 and 86 were available for mono- or combination therapy, respectively.

The median duration of HFS was shorter in the monotherapy group (28.0 days) compared to combination therapy (39.0 days). Nonetheless, the small number of patients has to be considered in this comparison (N = 19 and 30, respectively). The duration of HFS in all therapy groups is given in table 6. Patients with HFS had a longer duration of therapy, with, on average, 1 additional cycle (6.1 vs. 5.2 months and 8.3 vs. 7.3 cycles). No negative impact of HFS on the global QoL was detected. This could be partially due to the patients knowing that HFS is a predictive factor with regard to a potentially prolonged PFS.

Quality of Life

The QoL remained stable during the course of the investigation, which was in accordance with a good compliance. 53.9% of the patients (N = 169) admitted that the overall results of the therapy were as what they had expected or even better. 56.7% (N = 178) reported that the adverse effects were as expected or less severe. Patients with combination therapy appeared to feel better than patients under capecitabine alone. With regard to the respective drugs, this effect seemed most prominent in combination with trastuzumab. However, the patients in the trastuzumab group had been in much better condition at the beginning of the investigation, which

Table 7. Physician assessment of compliance and treatment outcomes

Parameter	Monotherapy (N = 346), n (%)	Combination therapy (N = 389), n (%)	Overall (N = 735), n (%)
Therapy overall	346 (100.0)	389 (100.0)	735 (100.0)
Excellent	9 (2.6)	1 (0.3)	10 (1.4)
Very good	41 (11.8)	48 (12.3)	89 (12.1)
Good	141 (40.8)	171 (44.0)	312 (42.4)
Moderate	112 (32.4)	125 (32.1)	237 (32.2)
Poor	37 (10.7)	31 (8.0)	68 (9.3)
Not specified	6 (1.7)	13 (3.3)	19 (2.6)
Efficacy	320 (100.0)	351 (100.0)	671 (100.0)
Excellent	21 (6.6)	11 (3.1)	32 (4.8)
Very good	30 (9.4)	37 (10.5)	67 (10.0)
Good	146 (45.6)	184 (52.4)	330 (49.2)
Moderate	85 (26.6)	90 (25.6)	175 (26.1)
Poor	38 (11.9)	29 (8.3)	67 (10.0)
Tolerability	324 (100.0)	361 (100.0)	685 (100.0)
Excellent	18 (5.6)	16 (4.4)	34 (5.0)
Very good	57 (17.6)	58 (16.1)	115 (16.8)
Good	168 (51.9)	188 (52.1)	356 (52.0)
Moderate	52 (16.0)	69 (19.1)	121 (17.7)
Poor	29 (9.0)	30 (8.3)	59 (8.6)
Compliance	301 (100.0)	327 (100.0)	628 (100.0)
Excellent	15 (5.0)	16 (4.9)	31 (4.9)
Very good	33 (11.0)	35 (10.7)	68 (10.8)
Good	219 (72.8)	243 (74.3)	462 (73.6)
Moderate	23 (7.6)	27 (8.3)	50 (8.0)
Poor	11 (3.7)	6 (1.8)	17 (2.7)

could have led to bias because of positive selection. The scores for physical, role and social function as well as for fatigue, nausea and vomiting, pain, dyspnea, sleep disturbances, and constipation had a rather steady course during the investigation. Fatigue was of higher seriousness than other parameters like nausea, vomiting, and constipation. Emotional function, anorexia, and financial difficulties slightly increased over time while cognitive function marginally decreased. A relevant increase during the investigation was detected for diarrhea and HFS. For all scales and single items, a possible bias due to declining questionnaire return rates has to be considered. 55.9% of the physicians (N = 411) classified the overall therapy as at least 'good' (table 7). The respective values for efficacy and tolerability were 64.0% and 73.8%. In addition, 89.3% of the doctors (N = 561) considered the patient compliance as good, very good, or excellent, which is a clear indicator of high patient satisfaction. This could be due to the favorable toxicity profile of capecitabine compared to other chemotherapies. The oral availability of this specific chemotherapeutic agent enables the patients to apply their medication at home, saving venous punctures and valuable lifetime. Occurrence of HFS did not lead to a reduction in QoL. The main reasons for discontinuation of treatment were progressive disease (36.3%) and death (8.3%). Moreover, 24% of the patients completed the investigation up to the 12th cycle, which also shows a high level of satisfaction and QoL.

Discussion

QoL data is mostly collected within clinical trials with stringent inclusion criteria which might not reflect the patient population in clinical routine settings. Therefore, the focus of the present investigation was the evaluation of QoL in patients with metastatic breast cancer during treatment with capecitabine in a routine setting. Data from this study confirmed former clinical investigations on the efficacy of capecitabine in the treatment of metastatic breast cancer [9–11] as well as colorectal cancer [12, 13]. These investigations unanimously attested a maintained or improved QoL during capecitabine therapy. In 35% of the patients, tumor remission was achieved, and the DCR was 64%. The response to capecitabine monotherapy was in the same range as for combination therapy. The median PFS reached 6.8 months and was comparable for both groups.

The QoL remained at the same level throughout the observation period, which is an important aspect for therapies that should be administered for longer terms. QoL is – besides survival and morbidity – the third column for drug assessments and has become a major focus of interest. A search in Medline rendered a yearly average of 100 clinical trial publications for the combined terms 'breast cancer' and 'quality of life' in the last 5 years, with a steady increase of all publications indexing these two terms, from 372 in 2005 to 678 in 2013.

The present study indicated that HFS did not lead to a reduction in QoL. The levels remained stable during the entire course of the investigation. Patients with HFS received lower daily dosages and had more therapeutic intermissions than those without HFS. Subsequently, the total dose applied was lower in these patients, but did not seem to cause a relevant underdosing. On the contrary, HFS appeared to be an indicator of cellular activity and response to capecitabine. Across all therapy lines, the efficacy of capecitabine was significantly better in patients with HFS than in patients without these symptoms: The median PFS was found to be longer, with 8.4 vs. 5.6 months (HR 0.60, 95% CI 0.49–0.74; $p < 0.0001$). This finding was consistent for all subgroups of monotherapy and the various combination therapies. Nonetheless, it has to be taken into account that no validated questionnaire for HFS is available. With respect to methodology, the internal dynamics of questionnaire responses and a possible selection bias should be taken into consideration. It is very likely that those patients who felt well with the study medication more frequently continued to answer questionnaires until the end of the investigation than dissatisfied patients, which might cause bias. Furthermore, the most limiting factor in the evaluation of none-interventional trials is the missing baseline evaluation. In the present study, 50% of the patients completed the first questionnaire after starting the medication, so that the baseline parameters may already have been influenced by the therapy and should therefore not be overemphasized.

The physicians' assessment of tolerability and safety of capecitabine was similar for the mono- and combination therapies. General condition, HER2 status, and tolerability were the most important criteria for the choice of capecitabine as therapy regimen. Age was just a secondary factor. The safety profile of capecitabine was confirmed to be acceptable. It could also be demonstrated that the most important combination therapies with capecitabine, i.e. bevacizumab, lapatinib, trastuzumab, and vinorelbine, were safe and well tolerated in everyday use. Only 11.9% of the patients discontinued their therapies because of adverse events. The most common adverse event that led to termination was HFS. However, no

negative impact of HFS on the global QoL could be detected, possibly in part due to the patients knowing that HFS is a predictive factor with regard to an increased DCR and prolonged PFS and overall survival, which has been confirmed during several investigations in colorectal cancer [14, 15] and also in metastatic breast cancer [16]. Compared to other side effects, physicians possibly accord a higher relevance to HFS than patients do. Patient compliance was good in all therapeutic regimens and was not impaired by the occurrence of HFS. The doctors' assessment of compliance was independent of the therapy modality (single agent or combination) and was in good accordance with the patients' responses.

It can be concluded that capecitabine therapy is a therapeutic option with a favorable risk-benefit profile. Patients who suffer from capecitabine-related HFS should be informed about the positive predictive character of this adverse effect. Subsequently, therapeutic adherence can be reinforced and patients will be motivated to continue with this useful therapy.

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Disclosure Statement

We declare the following conflicts of interest: V.M. has received speaker honoraria from Amgen, Celgene, Glaxo Smith Kline, Pierre-Fabre, Roche, and Janssen-Cilag. T.W.: Employee at Roche, stock ownership: Roche. C.C.S.: Speaker honoraria from Roche, Glaxo Smith Kline, Amgen, Advisory Board member: Roche. S.F.: Speaker honoraria from Amgen, Sanofi, Roche, Lilly and various other companies. M.Z.: Speaker honoraria: Roche, Boehringer, Pfizer, Advisory Board member: Roche, Pfizer, Lilly, Janssen. B.L.: Advisory Board member: Amgen. The remaining authors have declared no conflicts of interest.

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