Impact of disease progression on health-related quality of life in patients with metastatic breast cancer in the PRAEGNANT breast cancer registry

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BACKGROUND

In recent years, great advances have been made in treating advanced breast cancer. For the groups of patients with HER2-positive and with HER2-negative, hormone receptor-positive metastatic breast cancer, the introduction of pertuzumab and T-DM1 for HER2-positive disease and mTOR inhibition and recently for CDK4/6 inhibition has greatly improved progression free survival and for pertuzumab and T-DM1 also overall survival.

Progression-free survival (PFS) with the assumed therapy goal of delaying or preventing a deterioration of quality of life (QoL) is also considered an important patient-relevant objective. However "whether an improvement in PFS represents a direct clinical benefit or a surrogate for clinical benefit depends on the magnitude of the effect and the risk-benefit of the new treatment compared to available therapies".

For most clinicians, preventing tumor progression with acceptable toxicities is a relevant endpoint since tumor progression is assumed to be associated with increased symptoms and psychological stress, impairing health-related quality of life (HRQoLAim of our analysis was, therefore, to examine the extent to which disease progression impacts QoL in a metastatic breast cancer registry. Specifically, we test the hypothesis that progression is associated with differences in global health status. Further exploratory study aims are the differences in other domains/scales of the EORTC-QLQ C30 questionnaire in this context.

STUDY DESIGN AND METHODS

The PRAEGNANT study is conducted as a prospective diagnostic translational and multi-centric registry with a central documentation of patient and tumor characteristics and a central biomaterial archive for prospective molecular analyses. The Study network aims at registering 3500 breast cancer patients with advanced, incurable, metastatic disease.

Patient Selection

Patients were required to have at least two QoL assessments. Patients with disease progression were required to have a QoL assessment at least 14 days, but not longer than 6 months before progression was documented. Furthermore, these patients were required to have a QoL assessment at least 14 days after the progression but not longer than 6 months thereafter (no patient died within this interval). This produced a group of 76 patients with an observation time ranging from 83 to 628 days. Therefore, patients without disease progression needed to have at least two QoL assessments that were between 80 and 630 days apart.

Data collection

Clinical data were collected by trained and dedicated staff at the sites participating in the prospective PRAEGNANT study. These data are monitored using automated plausibility checks and through random on-site field monitoring.

ASSESSMENT OF QoL

Using the paper-based EORTC-QLQ-C30 Version 3.0 questionnaire, QoL was assessed. Furthermore, the EORTC-QLQ-BR23 and the EQ-5D-5L were distributed; however, the results of these questionnaires are not reported here. HRQoL questionnaires were distributed at the beginning of the study and study procedures required repeated distribution and completion every 3 months thereafter.

The EORTC QLQ-C30 is a 30-item questionnaire composed of a global QoL subscale, 5 multi-item functional subscales (physical, role, emotional, cognitive, and social functioning), 3 multi-item symptom scales (fatigue, nausea/vomiting, and pain), and 5 single-item symptom scales assessing other cancer-related symptoms (dyspnea, sleep disturbance, appetite loss, constipation, and diarrhea). The questionnaire consists of 4-point Likert scale items with responses from 'not at all' to 'very much' to assess functioning and symptoms and two 7-point Likert scale items for global health and overall QoL.

Responses to all items were converted to a 0–100 scale using a standard scoring. For functional and global QoL scales, higher scores represent a better level of functioning/QoL than lower scores; for symptom-oriented scales, higher scores represent greater symptom severity. For the single items, if two answers were given to a single question, the more severe answer was counted. If ≥50% of the questions were answered for the multi-item scales, the scale score was the mean score. If <50% of the questions in any scale were answered, the score was considered missing.

Primary endpoint

Minimally important deterioration (MID) of global QoL was defined as the lower limit of a small deterioration, i.e., at least a deterioration in global QoL score of five points. Deploying this approach, patients were divided into two groups, one with a MID and another without.

Statistical methods

Primary study aim was the association of MID of the global QoL status as assessed by the EORTC-QLQ-C30 with progression status. For that a logistic regression model was built with MID as the outcome and the following predictors: age at study entry (continuous), BMI (continuous), QoL assessment at baseline (continuous), time from first metastasis to QoL assessment and baseline (continuous), hormone receptor status (positive/negative), HER2 status (positive/negative), therapy at baseline (chemotherapy/anti-hormone therapy/everolimus plus and hormone therapy/other/unknown), therapy at follow-up (same categories), and progression (yes/no). Patients with missing outcome were excluded. Missing predictor values (except progression status) were imputed as done by Salmen et al. and continuous predictors were used as natural cubic spline functions.

Secondary study aim was to compare differences in all scales of the EORTC-QLQ-C30. The association between progression status and the QoL course was analyzed using linear mixed models, each with a specific scale as outcome, scale as outcome, "patient" as random effect, the aforementioned predictors as well as "time" (two time points), and the interaction between time and progression status as fixed effects. The random effect takes into account that each patient had repeated measures. The mean difference between the second and the first QoL measures adjusted for the other predictors was estimated for patients with and without progression using the linear mixed model. Furthermore, these linear mixed models were each compared with a reduced liner mixed model with the same predictors but without progression status and without the aforementioned interaction term, using a likelihood ratio test. The resulting p-values were adjusted for multiple testing according to Bonferroni-Holm. A significant p-value means that progression status was associated with QoL.

All tests were two-sided; a p-value of < 0.05 was regarded as statistically significant. Calculations were carried out using the R system for statistical computing (version 3.0.1; R Development Core Team, Vienna, Austria, 2013).

RESULTS

Patient characteristics and progression patterns

Patients who experienced progression were on average 59.8 (+/- 12.3), patients without on average 59.0 (+/-10.6) years old. Time from first metastasis to baseline QoL assessment was 984 (+/-1282) days in the group of patients with progression and 662 (+/-785) days in the group of patients without. The total interval between the two QoL assessments was 140 (+/-90) days for patients with and 258 (+/-128) days for patients without a progression. Ongoing therapies during the QoL assessment were similar among the two groups, except that the group with progression contained more patients with unknown therapy status. Detailed patient and disease characteristics are presented in **Table 1**.

Baseline QoL characteristics

Baseline QoL scores for domains/subscales are shown in **Table 2**. Domains/subscales according to patient groups (with versus without progression) were similar to the reference values provided by EORTC

Analysis of the primary study aim in the constructed logistic regression model (**not shown**) shows that QoL assessment at baseline was the strongest predictor for a MID in QoL. Furthermore, patients with progression had significantly more MIDs than those without. The adjusted odds ratio for progression status was 2.22 (95% – CI: 1.04 – 4.73). Although statistically nonsignificant, a higher BMI (OR per kg/m^2 = 1.04; 95% – CI: 1.00 – 1.09; P = 0.05) showed a trend towards a larger proportion of women with a MID of QoL.

Differences in Functional Scales

Although the primary study aim showed an influence of progression on MID, there was no difference in mean differences of global QoL scores (likelihood ratio test, uncorrected p = 0.24).

Differences in Symptom Scales

No statistically significant differences with regards to the symptom scales were found (likelihood ratio tests, uncorrected p-values). However, in patients with progression the burden for fatigue, nausea and vomiting, dyspnea, appetite loss and constipation seemed to be nominally higher but the pain scale and the insomnia scale indicated that these symptoms seemed to decrease more in patients with progression during the observation time (**Figure 2**).

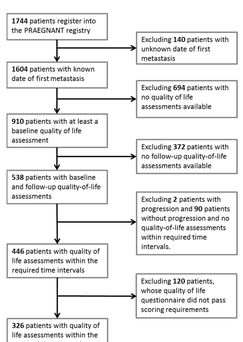

Figure 1: Patient distribution

Characteristic	Patients without progression		Patients with progression	
	n or mean	% or SD	n or mean	% or SD
Age	59.8	12.3	59.0	10.6
BMI	26.6	5.4	27.1	6.1
Time from first metastasis to baseline QoL (in days)	984	1282	662	785
Interval between HRQoL assessments (in days)	140	90	258	128
Hormone Receptor Status				
Negative	30	11.4	2	3.2
Positive	233	88.6	61	96.8
HER2 Status				
Negative	188	71.5	48	76.2
Positive	75	28.5	15	23.8
Therapy at baseline QOL				
Antihormone Therapy	75	28.5	21	33.3
Chemotherapy	76	28.9	25	39.7
Everolimus + AI	13	4.9	2	3.2
Other	46	17.5	10	15.9
Unknown	53	20.2	5	7.9
Therapy at second QOL				
Antihormone Therapy	67	25.5	12	19.0
Chemotherapy	74	28.1	30	47.6
Everolimus + AI	7	2.7	6	9.5
Other	32	12.2	6	9.5
Unknown	83	31.6	9	14.3
Deterioration of QoL*				
No	173	65.8	34	54.0
Yes	90	34.2	29	46.0

Table 1: Tumor characteristics for determining molecular subtypes (*defined as minimally important deterioration of QoL)

Group		OR (95% CI)	P
Progress			
	No	1 (Reference)	
	Yes	2.22 (1.04, 4.73)	0.04
Hormone Receptor Status	Negative	1 (Reference)	
	Positive	0.89 (0.37, 2.13)	0.79
HER2 Status			
	negative	1 (Reference)	
	positive	0.60 (0.33, 1.10)	0.10
Therapy at baseline			
	AH	1 (Reference)	
	Chemo	0.54 (0.25, 1.14)	0.10
	Everolimus	2.64 (0.74, 9.48)	0.14
	Other	1.21 (0.50, 2.92)	0.67
	Unknown	0.69 (0.31, 1.54)	0.37
Therapy at baseline			
	AH	1 (Reference)	
	Chemo	1.94 (0.86, 4.38)	0.11
	Everolimus	0.50 (0.10, 2.38)	0.38
	Other	1.18 (0.41, 3.45)	0.76
	Unknown	2.10 (1.01, 4.37)	0.05
Age		0.99 (0.97, 1.02)	0.55
BMI		1.04 (1.00, 1.09)	0.05
Interval between QoL assessments		1.00 (1.00, 1.00)	0.90
Time from first metastasis to baseline QoL		1.00 (1.00, 1.00)	0.98
QoL Score at baseline		1.04 (1.03, 1.06)	< 0.000001

Table 3: Logistic regression model for the association of minimally important difference between both time points

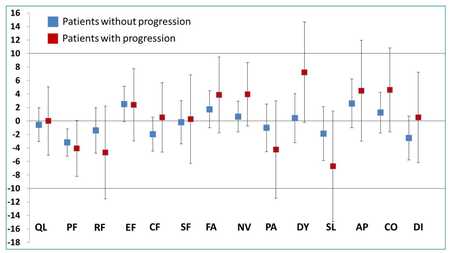

Figure 2: Overall change from baseline in EORTC QLQ-C30 scores for global QoL, functional and symptom scales.

Legend Figure 2: Changes from baseline in the patient-reported outcomes analysis population were determined with linear mixed models, each with a specific scale as outcome. Mean changes with 95% confidence intervals adjusted for covariates are shown. Data values are provided in Supplementary Table 2 (AP, appetite loss; CF, cognitive functioning; CO, constipation; DI, diarrhea; DY, dyspnea; EF, emotional functioning; FA, fatigue; NV, nausea and vomiting; PA, pain; PF, physical functioning; QL, global quality of life; RF, role functioning; SF, social functionng; SL, insomnia).

Deterioration of global QoL

Analysis of the primary study aim in the constructed logistic regression model (**Table 3**) shows that QoL assessment at baseline was the strongest predictor for a MID in QoL. Furthermore, patients with progression had significantly more MIDs than those without. The adjusted odds ratio for progression status was 2.22 (95% – CI: 1.04 – 4.73). Although statistically non-significant, a higher BMI (OR per kg/m^2 = 1.04; 95% – CI: 1.00 – 1.09; P = 0.05) showed a trend towards a larger proportion of women with a MID of QoL.

	Patients without progression		Patients with progression		
Domain/Scale	n	mean (SD)	n	mean (SD)	Reference Values Mean (SD)
Global QOL	306	56.8 (20.0)	65	52.2 (21.7)	60.2 (25.5)
Physical functioning	308	69.4 (21.9)	66	69.1 (22.3)	81.6 (18.7)
Role functioning	304	57.2 (31.2)	65	56.4 (28.8)	67.4 (31.1)
Emotional functioning	304	58.0 (26.1)	65	55.2 (23.2)	65.9 (24.6)
Cognitive functioning	306	74.9 (25.1)	66	75.8 (25.5)	80.5 (23.2)
Social functioning	305	61.0 (31.9)	65	60.8 (26.4)	74.2 (28.4)
Fatigue	306	46.7 (25.9)	64	48.9 (22.3)	36.3 (27.0)
Nausea/vomiting	308	8.9 (16.4)	64	8.6 (17.3)	10.3 (19.7)
Pain	307	37.8 (31.3)	65	43.6 (32.6)	30.9 (29.6)
Dyspnea	304	33.8 (32.2)	65	35.4 (32.7)	20.4 (28.2)
Insomnia	300	41.8 (33.5)	61	48.1 (30.7)	33.1 (32.6)
Appetite loss	305	17.5 (26.4)	64	22.4 (29.1)	21.7 (31.0)
Constipation	305	15.0 (27.1)	64	11.5 (20.8)	19.2 (28.8)
Diarrhea	306	18.4 (28.2)	64	14.6 (25.8)	5.8 (15.2)

Table 2: Baseline scores for EORTC QLQ-C30 and reference values

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DISCUSSION

In this retrospective analysis we could show that, in a higher percentage of metastatic breast cancer patients, a minimally important deterioration in HRQoL is associated with disease progression within a certain time interval. The adjusted odds ratio was significantly increased more than two-fold in patients with progression compared to patients without progression. Regarding mean differences between the two groups, however, no difference between patients with and without progression was observed. There seems to be a trend that physical functioning and role functioning are affected more in patients with progression than in those without. Regarding symptom scales, fatigue, nausea and vomiting, dyspnea, appetite loss, and constipation scores seemed to be higher in patients with a progression than in patients without.

Interestingly, pain and insomnia both were more reduced in patients with a disease progression. In our analysis – although not significant – the completion of the follow-up QoL assessment at the end of the observation time during chemotherapy indicated an almost twice as high odds ratio of experiencing a MID of QOL. Information on subsequent treatment lines after progression is not collected in most clinical trials. Therefore, the data generated in this study might be helpful for gaining knowledge about the course of therapy regardless of primary and secondary endpoints in clinical trials.

The broad acceptance of progression-free interval among clinicians is based upon the fact that tumor progression is often associated with worsening of symptoms and therefore QoL impairment. Our study adds to that evidence with study data not from a clinical trial.

There are several strengths and limitations to this study. One of the strengths is that current treatments from routine clinical practice were used in this breast cancer registry since data were collected between July 2014 and March 2017. Therefore, treatments such as pertuzumab, trastuzumab-emtansin, and everolimus are represented A strength, but also a limitation, is the fact that we included all subtypes of breast cancer in all therapies. On the one hand, we could show that progression is associated with MID independently of time since first metastasis or therapy under which the QOL questionnaire was completed. On the other hand, the sample size might be too low to assess whether progression is specifically important in subpopulations being treated with either chemotherapy, anti-hormone therapy, or anti-HER2 treatments. However, our analysis was adjusted for subtypes and therefore our findings should be applicable to all molecular subtypes.

CONCLUSION

We provide evidence that disease progression in patients with metastatic breast cancer has a significantly negative impact on HRQoL. This study emphasizes the relevance of delaying progression in order to maintain QoL. Whether these effects are the consequence of poorer medical condition due to increased tumor burden or the consequence of therapeutic side effects remains unclear. QoL assessments beyond tumor progression should constitute a standard instrument in breast cancer registries in order to generate information in addition to QoL assessments within clinical trials. In this context, the influence of therapeutic sequences should be evaluated in more detail.

RESEARCH SUPPORT

NOVARTIS Pfizer Celgene