

# Relationship between chemotherapy-induced adverse reactions and health-related quality of life in patients with breast cancer

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## Abstract

**Background and objectives:** Chemotherapy does not only affect cancer cells; it also affects, to a greater or lesser degree, all other cells in the body. This toxicity should be assessed according to its severity, frequency, and duration, taking into account objective and subjective dimensions in its assessment. This assessment is a highly relevant aspect when providing care to chemotherapy patients, mainly due to the impact of the treatment on the patient's quality of life, as well as the vital risk it may imply under certain circumstances. For all this, the objective of this study was to assess the relationship between chemotherapy-associated adverse reactions and health-related quality of life in breast cancer patients.

**Materials and methods:** With this purpose, a descriptive cross-sectional study was developed on 110 breast cancer patients who were treated with docetaxel, epirubicin, and cyclophosphamide.

**Results:** It is worth highlighting the negative effect of nausea, dysgeusia, peripheral neuropathy, loss of appetite, myalgia, and peripheral edema on the quality of life. Likewise, it is worth mentioning peripheral neuropathy as the toxicity that affects a greater number of quality-of-life indicators.

**Conclusions:** To sum up, it would be necessary to make health professionals aware of the importance of chemotherapy-associated adverse reactions.

**Abbreviations:** QT = chemotherapy, TEC = treatment scheme consisting of docetaxel, epirubicin and cyclophosphamide.

**Keywords:** breast cancer, drug-related side effects and adverse reactions, health-related quality of life, patient safety, quality of health care, toxicities

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The authors have no conflicts of interest to disclose.

All data generated or analyzed during this study are included in this published article [and its supplementary information files].

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## 1. Introduction

Chemotherapy (QT) does not only affect cancer cells; it also affects, to a greater or lesser degree, all other cells in the body. Specifically, the most affected cells by the cytotoxic effect of chemotherapy are those that share characteristics with tumor cells, especially high-speed cell division, such as hair follicles, bone marrow, digestive tract cells, and reproductive system cells. Therefore, chemotherapeutic treatments have a series of more or less serious effects on the rest of the body: These are called side effects or adverse reactions.<sup>[1]</sup>

The World Health Organization defines an Adverse Drug Reaction as a response to a medicine which is noxious and unintended, and which occurs at doses normally used in man for prophylaxis, diagnosis, or therapy of disease or for the modification of physiologic function.

This toxicity should be assessed according to its severity, frequency, and duration, taking into account objective and subjective dimensions in its assessment. The former include those that can be evaluated by physical examination or laboratory tests, while the latter would include those that cause symptoms that are not related to evaluable physical signs or analytical alterations, and they must be assessed exclusively at the medical consultation.

The reason for assessing chemotherapy-associated toxicity is because many of the adverse reactions could be avoided or minimized by performing a thorough evaluation after each chemotherapy cycle.<sup>[2,3]</sup> The possibility of avoiding or minimizing

chemotherapy-associated toxicity is a highly relevant aspect in cancer patient care, mainly because of the impact it poses on the patient's quality of life, as well as the vital risk it can cause under some circumstances.<sup>[3-6]</sup>

Oncologists generally maintain, reduce, or delay administration of the next chemotherapy cycle based on the collected toxicity.<sup>[2]</sup> Underestimation of adverse reactions can lead to lack of dose adjustments where appropriate and, subsequently, the unadjusted dose may reproduce or increase the complications experienced in the previous cycle, leading to increased morbidity, avoidable hospitalisations, or premature removal of chemotherapy.<sup>[3,4,7,8]</sup>

In addition, patients underestimate adverse reactions by considering them as part of the treatment, and even as a sign that the treatment is "working."<sup>[9-11]</sup> Therefore, as Salsman et al<sup>[9]</sup> demonstrate in a descriptive comparative study, although patients perceive these adverse reactions as disabling, they often understand them as a normal part of the treatment. Furthermore, patients have to wait until their next appointment to report any toxicity episodes, so incidence and intensity are likely to be subjected to memory biases.

On the contrary, physicians strongly support the need to treat these toxicities and the relevance of professional ability for the same purpose.<sup>[9]</sup> The resulting under-registration of frequency and intensity contradicts doctors' belief that if toxicities are a problem, their patients will inform them. In general, oncology health workers often underestimate the incidence of chemotherapy-associated toxicities.<sup>[3,11,12]</sup> By contrast, the holistic application of day hospital nursing care implies a greater knowledge of these adverse reactions.<sup>[13]</sup>

However, adverse reactions maintained during chemotherapy cycles can imply a major impact on the quality of life of the cancer patient by altering metabolic balance, decreasing mental performance, degenerating self-care and functional capacity, and even increasing the risk of withdrawal of the chemotherapy treatment.<sup>[3,10,14,15]</sup>

In contrast, there are few studies<sup>[16]</sup> that link chemotherapy-associated toxicities with the patients' quality of life. Most of them are related to nausea and vomiting, lymphedema, pain, and symptoms of premature menopause.<sup>[16,17]</sup> However, they barely collect other toxicities, not least important for the patient, such as peripheral neuropathy.<sup>[18]</sup>

For example, the treatment scheme consisting of docetaxel, epirubicin, and cyclophosphamide (TEC) has favorable clinical outcomes for breast cancer patients.<sup>[19-24]</sup> In contrast, this scheme is highly toxic for the patient's body, and it is necessary to monitor the toxicities that occur after the chemotherapy cycles.<sup>[25,26]</sup> This control would be aimed at reducing the dose at the optimal time to avoid overdosing.

Thus, it is important to know, collect, and protocolize clinical performance in each of the side effects associated with each type of chemotherapy drug.

Therefore, the objective of this study was to analyze the relationship between chemotherapy-associated adverse reactions and the health-related quality of life of breast cancer patients.

## 2. Methods

### 2.1. Design

Descriptive cross-sectional study. Breast cancer patients in treatment with first-line neoadjuvant or adjuvant chemotherapy

with docetaxel, epirubicin and cyclophosphamide were studied. The total study period was between May 2012 and August 2014, in a second-level hospital (medium level of complexity).

### 2.2. Participants

The inclusion criteria implied all breast cancer patients under chemotherapeutic treatment, being it neoadjuvant or adjuvant, with the TEC regimen+filgrastim or pegfilgrastim colony stimulating factor+triple antiemetic therapy with dexamethasone, aprepitant, and ondansetron, and who had at least undergone 1 cycle through this scheme. All patients who, meeting the inclusion criteria, had previously responded to the questionnaire developed in the study, as well as all patients who were starting their first treatment cycle, were excluded.

For the calculation of the required sample size, the total number of patients with these characteristics initiating their treatment for 1 year through the TEC scheme (approximately 60) was taken into account, with a representative sample size of 52 estimated patients, a 95% confidence level, and a maximum estimate error of 5%. However, it was calculated that to estimate the differences in quality of life with, at least, an average effect size (Cohen d greater than or equal to 0.3), based on a 95% confidence level, a statistical power of 10%, and an accuracy of 5 points, at least 78 subjects were required. Finally, taking into account a low proportion of losses in responses (fruit of a previously conducted pilot study), a minimum sample size of 80 patients was established. The questionnaire was given randomly, according to a cluster scheme, in 1 of the 6 treatment cycles so, when homogeneously stratified by therapy cycles, a minimum sample of 10/11 subjects in each of the cycles was estimated.

The final sample consisted of 112 women with breast cancer who met the established inclusion criteria, thus exceeding the minimum established sample and collecting, in most cycles, more than the 10/11 previously established patients. All the participants completed the 6 chemotherapy cycles. Two patients eventually declined to participate in the study, so their data were omitted, and this resulted in a final sample of 110 patients.

### 2.3. Instruments

An "ad hoc" questionnaire was prepared for the patient, including all common nonhematological adverse reactions observed with the TEC scheme in previous clinical trials,<sup>[24,27]</sup> as well as the specification sheet of each drug, collected in the Spanish Agency of Medicines and Medical Products. These toxicities were subsequently delivered, for external validation using a Delphi technique, to 11 oncologists related to breast cancer to specify the estimated frequency for each toxicity. In addition, they were asked whether they considered that there was any other adverse reaction to be taken into account. The result was positive for the prepared questionnaire.

To obtain the verification of validity, the questionnaire was subjected to previous study. To this end, the questionnaire was provided to an initial sample of 12 breast cancer patients undergoing the TEC scheme and to 5 oncologists who treated breast cancer to assess, on the one hand, the understanding of the questionnaire and, on the other hand, the completeness in the collection of the most common adverse symptomatology in this type of treatment. The results showed the adequacy of the questionnaire for the proposed purposes.

For the assessment of health-related quality of life, the EuroQol-5D questionnaire<sup>[28]</sup> was used for presenting an A level of recommendation and because it best suited the needs of the study. Several studies supported the validity of the EQ-5D-3L index.<sup>[29–31]</sup>

#### 2.4. Procedure

Medical prescriptions have been reviewed daily by locating the patients under study. These patients had to pre-enter the oncology consultation and then go to the Day Hospital to receive their treatment. A day hospital is a health-centered structure through which the patient is admitted for a planned number of hours during which they receive specialized treatment from the specialists. These treatments require monitoring or medical equipment that must be handled within the medical premises. At the end of the care, the patient returns home. Then, at the Day Hospital, each patient was given the questionnaire, that is, the subject of study, with which she responded to the toxicities suffered in the previous 21 days, that is, in the previous cycle. The questionnaire was given randomly in 1 of the 6 treatment cycles. The objective and how to appropriately answer the questions were explained in detail. Once completed, the patient was excluded for the following cycles. In addition, the help of nurses was available at all times to help with any doubts when filling the questionnaire. All the patients signed the informed consent after receiving information on it and all the possible doubts had been resolved by the main researcher.

#### 2.5. Data analysis

Descriptive statistics, contrast tests of proportions ( $\chi^2$  test) and means (Student *t* test and Mann–Whitney *U* test), agreement level contrast (Cohen Kappa), and effect size assessment techniques (Phi, Cramer V, and Cohen *d*) were used. The statistical software used was IBM SPSS Statistics 22.0 and EQS 6.2. In all cases, a statistical significance of  $P < .05$  was required.

#### 2.6. Ethical aspects

The study was carried out, for the development and follow-up of the clinical research, following the “Ethical Principles for Medical Research with Humans” compiled in the latest version of the Helsinki Declaration (Edinburgh version, October 2000). This study was approved by the Research Ethics Committee of the province of Huelva on May 2013, with research code: PRI-TEC-2012-01. In all cases, the anonymity of the participants was guaranteed. In addition, an informed written consent was obtained prior to participation, and the research protocol included the approval of the Huelva Biomedical Research Ethics Committee. In addition, the basic Law 41/2002 regulating patient autonomy and rights and obligations in the field of information and clinical documentation was implemented.

### 3. Results

The final sample consisted of 110 women. The profile of the study participant is a woman with an average age of 49.61 (typical deviation of 8.28 years and with a range of age from 29 to 68 years), married (78.9%), with children (83.5%), who is usually accompanied during the consultation (96.2%). All the patients completed the 6 chemotherapy cycles.

**Table 1**

**Description of the sample in terms of treatment characteristics.**

		Number of patients	% of patients
Cycle	First cycle	29	26.4%
	Second cycle	29	26.4%
	Third cycle	19	17.3%
	Fourth cycle	24	21.8%
	Fifth cycle	9	8.2%
Adjuvancy	Neoadjuvancy	49	44.5%
	Adjuvancy	61	55.5%
Dose readjustment	No	59	52.3%
	Yes	51	47.7%
Hospitalisation	No	74	66.4%
	Yes	36	33.6%

The type of received treatment was relatively homogeneous between neoadjuvant (presurgery) and adjuvant (postsurgery) treatment, with results of about 50%. Specifically, the percentage of patients who were receiving the treatment as a neoadjuvant was 44.5%, and 55.5% as adjuvant. The majority of patients responded to the questionnaire to include the adverse reactions suffered after the 21 days that lasted their first (26.4%) and second (26.4%) cycle of chemotherapy. The cycle with the lowest response rate was the fifth one (8.2%), this being the last data collection cycle (Table 1).

On the other hand, 52.3% of patients maintained the same dose as the one prescribed at the beginning of the first chemotherapy cycle. However, in 47.7% of patients, this dose had to be reduced in 20% due to hematological toxicity (neutropenia) or nonhematological toxicity (peripheral neuropathy, diarrhoea, etc). Specifically, 62.5% of patients started their second chemotherapy cycle with a reduced dose.

Likewise, 66.4% of patients did not attend an emergency department during the whole process. However, 33.6% of those attending the emergency department were eventually admitted to hospital for an average of 3 days. 56.7% were admitted due to toxicities suffered during the first chemotherapy cycle.

As for the relationship between the quality of life and the specific chemotherapy cycle, no significant difference was found ( $P = .154$ ). However, by analyzing the effect size, a great trend is observed between the quality of life in the first cycle and the second cycle (Cohen  $d = 0.81$ ). In particular, there is a higher quality of life during the first cycle (mean = 15.16) than during the second cycle (mean = 13.81). In all other cycles, the effect size is not significant.

Likewise, looking at the different indicators of quality of life on the general population of the study, it is observed that most patients consider that they have no problems with walking (73.4%), self-care (95.4%), everyday activities (53.2%) and, in addition, they are not anxious or depressed (63.9%). In contrast, 56.9% of patients feel moderate pain or discomfort, and 67.9% perceive their overall health worse than they did a year ago.

On the other hand, it is important to note that 3 patients had to be in bed and 1 patient was unable to perform daily activities. In addition, 4 patients felt a lot of pain or discomfort in that cycle, and 5 patients felt very anxious or depressed.

#### 3.1. Gastrointestinal toxicity

Statistically significant differences have been established for the relationship nausea-quality of life [ $U(77) = 440$ ,  $P = .020$ ], with

**Table 2****Distribution of the different indicators of health-related quality of life based on gastrointestinal toxicity indicators.**

		Vomiting		Nausea		Diarrhoea		Constipation	
		No	Yes	No	Yes	No	Yes	No	Yes
Mobility	I have no problems walking	73.2% (71)	72.7% (8)	77.8% (28)	70.8% (51)	76.8% (43)	69.8% (37)	71.6% (48)	75.0% (30)
	I have some problems walking	23.7% (23)	27.3% (3)	22.2% (8)	25.0% (18)	21.4% (12)	26.4% (14)	25.4% (17)	22.5% (9)
	I have to stay in bed	3.1% (3)	0.0% (0)	0.0% (0)	4.2% (3)	1.8% (1)	3.8% (2)	3.0% (2)	2.5% (1)
Personal care	I have no problems with personal care	95.9% (93)	90.0% (9)	97.2% (35)	94.4% (67)	92.9% (52)	98.1% (51)	93.9% (62)	97.5% (39)
	I have some problems washing myself and getting dressed	4.1% (4)	10.0% (1)	2.8% (1)	5.6% (4)	7.1% (4)	1.9% (1)	6.1% (4)	2.5% (1)
	I cannot wash myself or get dressed	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)
Daily activities	I have no problems performing my daily activities	53.6% (52)	45.5% (5)	55.6% (20)	51.4% (37)	58.9% (33)	47.2% (25)	50.7% (34)	55.0% (22)
	I have some problems performing my daily activities	45.4% (44)	54.5% (6)	44.4% (16)	47.2% (34)	41.1% (23)	50.9% (27)	47.8% (32)	45.0% (18)
	I cannot perform my daily activities	1.0% (1)	0.0% (0)	0.0% (0)	1.4% (1)	0.0% (0)	1.9% (1)	1.5% (1)	0.0% (0)
Pain/discomfort	I have no pain or discomfort	42.3% (41)	18.2% (2)	52.8% (19)	33.3% (24)	48.2% (27)	30.2% (16)	38.8% (26)	42.5% (17)
	I have moderate pain or discomfort	54.6% (53)	72.7% (8)	47.2% (17)	61.1% (44)	50.0% (28)	64.2% (34)	56.7% (38)	55.0% (22)
Anxiety/depression	I have a lot of pain or discomfort	3.1% (3)	9.1% (1)	0.0% (0)	5.6% (4)	1.8% (1)	5.7% (3)	4.5% (3)	2.5% (1)
	I am not anxious or depressed	61.9% (60)	80.0% (8)	80.6% (29)	54.9% (39)	69.6% (39)	57.7% (30)	66.7% (44)	57.5% (23)
	I am moderately anxious or depressed	34.0% (33)	10.0% (1)	19.4% (7)	38.0% (27)	26.8% (15)	36.5% (19)	30.3% (20)	35.0% (14)
Health status	I am very anxious or depressed	4.1% (4)	10.0% (1)	0.0% (0)	7.0% (5)	3.6% (2)	5.8% (3)	3.0% (2)	7.5% (3)
	Better	10.1% (7)	0.0% (0)	8.0% (2)	9.6% (5)	8.3% (3)	9.5% (4)	6.3% (3)	14.3% (4)
	Same	23.2% (16)	25.0% (2)	36.0% (9)	17.3% (9)	13.9% (5)	31.0% (13)	20.8% (10)	28.6% (8)
	Worse	66.7% (46)	75.0% (6)	56.0% (14)	73.1% (38)	77.8% (28)	59.5% (25)	72.9% (35)	57.1% (16)
				Mucositis		Dysgeusia		Loss of appetite	
				No	Yes	No	Yes	No	Yes
Mobility	I have no problems walking			75.8% (47)	69.6% (32)	92.3% (12)	70.8% (68)	80.0% (44)	66.7% (36)
	I have some problems walking			22.6% (14)	26.1% (12)	7.7% (1)	26.0% (25)	18.2% (10)	29.6% (16)
	I have to stay in bed			1.6% (1)	4.3% (2)	0.0% (0)	3.1% (3)	1.8% (1)	3.7% (2)
Personal care	I have no problems with personal care			96.8% (60)	93.3% (42)	92.3% (12)	95.8% (91)	96.4% (53)	94.3% (50)
	I have some problems washing myself and getting dressed			3.2% (2)	6.7% (3)	7.7% (1)	4.2% (4)	3.6% (2)	5.7% (3)
	I cannot wash myself or get dressed			0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)
Daily activities	I have no problems performing my daily activities			54.8% (34)	50.0% (23)	76.9% (10)	50.0% (48)	65.5% (36)	40.7% (22)
	I have some problems performing my daily activities			43.5% (27)	50.0% (23)	23.1% (3)	49.0% (47)	34.5% (19)	57.4% (31)
	I cannot perform my daily activities			1.6% (1)	0.0% (0)	0.0% (0)	1.0% (1)	0.0% (0)	1.9% (1)
Pain/discomfort	I have no pain or discomfort			46.8% (29)	30.4% (14)	84.6% (11)	33.3% (32)	49.1% (27)	29.6% (16)
	I have moderate pain or discomfort			51.6% (32)	63.0% (29)	15.4% (2)	62.5% (60)	50.9% (28)	63.0% (34)
	I have a lot of pain or discomfort			1.6% (1)	6.5% (3)	0.0% (0)	4.2% (4)	0.0% (0)	7.4% (4)
Anxiety / depression	I am not anxious or depressed			66.1% (41)	60.0% (27)	84.6% (11)	61.1% (58)	70.9% (39)	56.6% (30)
	I am moderately anxious or depressed			33.9% (21)	28.9% (13)	15.4% (2)	33.7% (32)	27.3% (15)	35.8% (19)
	I am very anxious or depressed			0.0% (0)	11.1% (5)	0.0% (0)	5.3% (5)	1.8% (1)	7.5% (4)
Health status	Better			10.9% (5)	6.5% (2)	16.7% (1)	8.3% (6)	10.3% (4)	7.7% (3)
	Same			23.9% (11)	22.6% (7)	50.0% (3)	20.8% (15)	35.9% (14)	10.3% (4)
	Worse			65.2% (30)	71.0% (22)	33.3% (2)	70.8% (51)	53.8% (21)	82.1% (32)

In parentheses: number of patients.

an average effect size (Cohen  $d=0.56$ ). In particular, worse quality-of-life indicators are observed in those patients who report having suffered nausea (mean = 13.88), as compared with those who do not have this symptom (mean = 14.88). In addition, when analyzing each of the quality-of-life components, it is observed that patients with nausea have worse anxiety or depression indicators [ $\chi^2(2)=7.600$ ,  $P=.022$ , Cramer  $V=0.267$ ]. In particular, 54.9% of patients with nausea showed no

anxiety or depression indicators, as compared with 80.6% of patients who did not present this toxicity (Table 2).

As for vomiting, diarrhea, constipation, and mucositis, no statistically significant differences have been found in relation to the quality of life, and the effect size has been negligible, except for mucositis, where there is a small size effect (Cohen  $d=0.46$ ). It has not been possible to establish its influence on each of the quality-of-life components.

**Table 3****Distribution of the different indicators of health-related quality of life based on dermatological toxicity indicators.**

		Hands/feet skin reaction		Nail toxicity		Skin allergies	
		No	Yes	No	Yes	No	Yes
Mobility	I have no problems walking	70.4% (57)	81.5% (22)	73.0% (54)	73.5% (25)	68.6% (59)	90.5% (19)
	I have some problems walking	25.9% (21)	18.5% (5)	24.3% (18)	23.5% (8)	27.9% (24)	9.5% (2)
	I have to stay in bed	3.7% (3)	0.0% (0)	2.7% (2)	2.9% (1)	3.5% (3)	0.0% (0)
Personal care	I have no problems with personal care	95.1% (77)	96.2% (25)	95.9% (70)	94.1% (32)	94.2% (81)	100.0% (20)
	I have some problems washing myself and getting dressed	4.9% (4)	3.8% (1)	4.1% (3)	5.9% (2)	5.8% (5)	0.0% (0)
Daily activities	I cannot wash myself or get dressed	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)
	I have no problems performing my daily activities	50.6% (41)	59.3% (16)	59.5% (44)	41.2% (14)	51.2% (44)	61.9% (13)
	I have some problems performing my daily activities	49.4% (40)	37.0% (10)	39.2% (29)	58.8% (20)	47.7% (41)	38.1% (8)
Pain/discomfort	I cannot perform my daily activities	0.0% (0)	3.7% (1)	1.4% (1)	0.0% (0)	1.2% (1)	0.0% (0)
	I have no pain or discomfort	42.0% (34)	29.6% (8)	44.6% (33)	29.4% (10)	37.2% (32)	47.6% (10)
	I have moderate pain or discomfort	55.6% (45)	63.0% (17)	51.4% (38)	67.6% (23)	58.1% (50)	52.4% (11)
Anxiety / depression	I have a lot of pain or discomfort	2.5% (2)	7.4% (2)	4.1% (3)	2.9% (1)	4.7% (4)	0.0% (0)
	I am not anxious or depressed	63.0% (51)	65.4% (17)	65.8% (48)	61.8% (21)	59.3% (51)	80.0% (16)
	I am moderately anxious or depressed	33.3% (27)	26.9% (7)	28.8% (21)	35.3% (12)	34.9% (30)	20.0% (4)
Health status	I am very anxious or depressed	3.7% (3)	7.7% (2)	5.5% (4)	2.9% (1)	5.8% (5)	0.0% (0)
	Better	8.6% (5)	10.5% (2)	12.7% (7)	0.0% (0)	6.3% (4)	25.0% (3)
	Same	24.1% (14)	21.1% (4)	21.8% (12)	27.3% (6)	26.6% (17)	8.3% (1)
	Worse	67.2% (39)	68.4% (13)	65.5% (36)	72.7% (16)	67.2% (43)	66.7% (8)

In parentheses: number of patients.

In terms of loss of appetite, statistically significant differences have been found [ $U(78)=455, P=.002$ ], with an average effect size (Cohen  $d=0.77$ ). In particular, worse quality-of-life indicators are observed in patients who report loss of appetite (mean=13.56), as compared with those who do not show this problem (mean=14.87).

Based on the influence on each of the quality-of-life components, it is observed that patients with loss of appetite have worse indicators regarding daily activities [ $\chi^2(2)=7.251, P=.027$ , Cramer  $V=0.258$ ], pain or discomfort [ $\chi^2(2)=7.386, P=.025$ , Cramer  $V=0.260$ ], and general health status [ $\chi^2(2)=7.981, P=.018$ , Cramer  $V=0.320$ ].

Finally, dysgeusia show statistically significant differences [ $U(78)=107, P=.038$ ] and a large effect size (Cohen  $d=0.89$ ). In particular, worse quality-of-life outcomes are shown in patients with taste impairment (mean=14.10), as compared with those who do not show this alteration (mean=15.67).

In addition, when analyzing each of the quality-of-life components, it is observed that patients with dysgeusia have worse pain or discomfort indicators [ $\chi^2(2)=12.643, P=.002$ , Cramer  $V=0.341$ ].

### 3.2. Dermatological toxicity

In terms of dermatological toxicities, no statistically significant differences in skin reaction in hands and/or feet and in impaired nails have been found. In both toxicities, the effect size has been negligible. Likewise, these dermatological toxicities have not shown any statistical relationship with the different quality-of-life components.

In contrast, regarding skin allergies, there are statistically significant differences [ $U(76)=213, P=.014$ ] and a large effect size (Cohen  $d=0.88$ ). In particular, better quality-of-life indicators are shown in patients with skin allergies (mean=15.50), as compared with those who do not refer this symptom (mean=13.95). No differences have been found between each of

the quality-of-life components. However, by analyzing the effect size, differences can be found regarding the general health state [ $\chi^2(2)=5.275, P=.072$ , Cramer  $V=0.263$ ]. In particular, 66.7% of patients with skin allergies show a worse general health status, as compared with 67.2% of patients without this toxicity (Table 3).

### 3.3. Neurological toxicity

Peripheral neuropathy has been contrasted with the quality of life, finding statistically significant differences [ $U(77)=185, P=.000$ ] and also a large effect size (Cohen  $d=1.34$ ). In particular, worse health-related quality of life indicators are found in patients who claim to have peripheral neuropathy (mean=12.53), as compared with those who do not (mean=14.68).

Subsequently, as shown in Table 4, it is observed that patients with peripheral neuropathy have worse personal care indicators [ $\chi^2(1)=4.608, P=.032$ , Cramer  $V=0.208$ ], daily activities [ $\chi^2(2)=9.525, P=.009$ , Cramer  $V=0.297$ ], pain or discomfort [ $\chi^2(2)=11.725, P=0.003$ , Cramer  $V=0.329$ ], and anxiety or depression [ $\chi^2(2)=6.032, P=0.049$ , Cramer  $V=0.237$ ].

### 3.4. Pain-related toxicity

As for headaches, abdominal pain, and joint pain, no statistically significant differences have been found, and the effect size is small. On the other hand, when analyzing each of the quality-of-life components, no difference can be found as regards the presence or absence of these toxicities.

In contrast, regarding abdominal pain, there are differences as for pain or discomfort [ $\chi^2(2)=5.118, P=0.077$ , Cramer  $V=0.218$ ] and general health status [ $\chi^2(2)=3.206, P=.201$ , Cramer  $V=0.204$ ]. In terms of joint pain, there are differences in pain or discomfort indicators [ $\chi^2(2)=15.368, P=.000$ , Cramer  $V=0.377$ ].

**Table 4****Distribution of the different indicators of health-related quality of life based on neurological toxicity indicators.**

		Peripheral neuropathy	
		No	Yes
Mobility	I have no problems walking	76.2% (64)	62.5% (15)
	I have some problems walking	21.4% (18)	33.3% (8)
	I have to stay in bed	2.4% (2)	4.2% (1)
Personal care	I have no problems with personal care	97.6% (82)	87.0% (20)
	I have some problems washing myself and getting dressed	2.4% (2)	13.0% (3)
	I cannot wash myself or get dressed	0.0% (0)	0.0% (0)
Daily activities	I have no problems performing my daily activities	59.5% (50)	29.2% (7)
	I have some problems performing my daily activities	40.5% (34)	66.7% (16)
	I cannot perform my daily activities	0.0% (0)	4.2% (1)
Pain/discomfort	I have no pain or discomfort	46.4% (39)	16.7% (14)
	I have moderate pain or discomfort	52.4% (44)	70.8% (17)
	I have a lot of pain or discomfort	1.2% (1)	12.5% (3)
Anxiety/depression	I am not anxious or depressed	67.9% (57)	47.8% (11)
	I am moderately anxious or depressed	29.8% (25)	39.1% (9)
	I am very anxious or depressed	2.4% (2)	13.0% (3)
Health status	Better	10.0% (6)	5.9% (1)
	Same	28.3% (17)	
	Worse	61.7% (3)	88.2% (15)

In parentheses: number of patients.

As for muscle pain, statistically significant differences have been found [U (77)=436,  $P=.003$ ], and the effect size is moderate (Cohen  $d=0.76$ ). In particular, worse quality-of-life indicators are found in those patients with myalgia (mean = 13.6, 9), as compared with those who do not show this symptom (mean = 15.00). Then, when analyzing each of the quality-of-life components, it is observed that patients with myalgia have worse pain or discomfort [ $\chi^2(2)=16.166$ ,  $P=.000$ , Cramer  $V=0.387$ ] and general health status indicators [ $\chi^2(2)=7.831$ ,  $P=.020$ , Cramer  $V=0.319$ ] (Table 5).

### 3.5. Eye toxicity

Regarding conjunctivitis, no statistically significant differences have been found, but an appropriate, although small, effect size is shown (Cohen  $d=0.35$ ). Regarding this toxicity, worse quality-of-life indicators are observed in patients with the conjunctivitis (mean = 13.83), as compared with those who do not show this symptom (mean = 14.46).

By analyzing each of the quality-of-life components, no statistically significant difference has been found between them. However, by analyzing the effect size, differences in the general health status are found [ $\chi^2(2)=3.337$ ,  $P=.189$ , Cramer  $V=0.207$ ]. In particular, 80.0% of patients with conjunctivitis rate their general health status as worse, as compared with 60.4% of patients who do not have this eye toxicity (Table 6).

### 3.6. Constitutional symptoms

The presence of asthenia has then been contrasted with the quality of life, where no statistically significant differences have been found and the effect size has been moderate (Cohen  $d=0.64$ ). In particular, worse quality-of-life indicators are found in those patients who refer asthenia (mean = 14.09), as compared with those who do not show this toxicity (mean = 15.25).

On the other hand, when analyzing each of the quality-of-life components, it is observed that patients with asthenia have worse

mobility [ $\chi^2(2)=11.442$ ,  $P=.003$ , Cramer  $V=0.325$ ], daily activities [ $\chi^2(2)=6.137$ ,  $P=.046$ , Cramer  $v=0.238$ ], and pain or discomfort indicators [ $\chi^2(2)=6.762$ ,  $P=.034$ , Cramer  $V=.250$ ] (Table 7).

### 3.7. Lymphatic system toxicity

In terms of toxicity affecting the lymphatic system, peripheral edema, statistically significant differences, and a large effect size have been found (Cohen  $d=0.88$ ). In particular, patients with peripheral edema (mean = 13.20) show worse quality-of-life indicators than those without this toxicity (mean = 14.69).

Then, when analyzing each of the quality-of-life components, it is observed that patients with peripheral edema have worse mobility [ $\chi^2(2)=19.875$ ,  $P=.000$ , Cramer  $V=0.429$ ], pain or discomfort [ $\chi^2(2)=9.875$ ,  $P=.007$ , Cramer  $V=0.302$ ], and general health status indicators [ $\chi^2(2)=7.096$ ,  $P=.029$ , Cramer  $V=0.304$ ] (Table 8).

Correlations between adverse reactions and health-related quality of life are summarized in Table 9.

## 4. Discussion

Chemotherapy treatments are related to major toxicities that must be closely monitored by the doctor at each of the patient's consultations, prior to the administration of the next chemotherapy cycle, in a similar way to the collection of toxicities in the context of a clinical trial. However, in standard clinical practice, the patient's assumption that toxicities are unavoidable and intrinsic to the treatment makes the collection of nonhematological adverse reactions incomplete.

Meanwhile, as Priestman and Baum<sup>[28]</sup> demonstrated in 1976, the influence of adverse reactions on the quality of life of cancer patients is highly relevant. There are studies<sup>[32]</sup> that show that low quality of life negatively predisposes to the onset of certain diseases, including breast cancer. Therefore, it can be concluded

**Table 5****Distribution of the different indicators of health-related quality of life based on pain-related toxicity indicators.**

		Headache		Abdominal pain		Joint pain		Muscle pain	
		No	Yes	No	Yes	No	Yes	No	Yes
Mobility	I have no problems walking	68.0% (34)	77.6% (45)	72.7% (48)	73.8% (31)	80.5% (33)	68.7% (46)	80.0% (36)	69.8% (44)
	I have some problems walking	30.0% (15)	19.0% (11)	24.2% (16)	23.8% (10)	17.1% (7)	28.4% (19)	17.8% (8)	27.0% (17)
	I have to stay in bed	2.0% (1)	3.4% (2)	3.0% (2)	2.4% (1)	2.4% (1)	3.0% (2)	2.2% (1)	3.2% (2)
Personal care	I have no problems with personal care	98.0% (49)	93.0% (53)	95.5% (63)	95.1% (39)	97.6% (40)	93.9% (62)	95.6% (43)	95.2% (59)
	I have some problems washing myself and getting dressed	2.0% (1)	7.0% (4)	4.5% (3)	4.9% (2)	2.4% (1)	6.1% (4)	4.4% (2)	4.8% (3)
	I cannot wash myself or get dressed	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)
Daily activities	I have no problems performing my daily activities	50.0% (25)	55.2% (32)	59.1% (39)	42.9% (18)	58.5% (24)	49.3% (33)	64.4% (29)	46.0% (29)
	I have some problems performing my daily activities	50.0% (25)	43.1% (25)	40.9% (27)	54.8% (23)	41.5% (17)	49.3% (33)	35.6% (16)	52.4% (33)
	I cannot perform my daily activities	0.0% (0)	1.7% (1)	0.0% (0)	2.4% (1)	0.0% (0)	1.5% (1)	0.0% (0)	1.6% (1)
Pain/discomfort	I have no pain or discomfort	48.0% (24)	32.8% (19)	47.0% (31)	28.6% (12)	63.4% (26)	25.4% (17)	62.2% (28)	23.8% (15)
	I have moderate pain or discomfort	48.0% (24)	63.8% (37)	51.5% (34)	64.3% (27)	34.1% (14)	70.1% (47)	35.6% (16)	71.4% (45)
	I have a lot of pain or discomfort	4.0% (2)	3.4% (2)	1.5% (1)	7.1% (3)	2.4% (1)	4.5% (3)	2.2% (1)	4.8% (3)
Anxiety/depression	I am not anxious or depressed	66.0% (33)	61.4% (35)	72.7% (48)	48.8% (20)	61.0% (25)	65.2% (43)	68.9% (31)	59.7% (37)
	I am moderately anxious or depressed	30.0% (15)	33.3% (19)	22.7% (15)	46.3% (19)	36.6% (15)	28.8% (19)	26.7% (12)	35.5% (22)
	I am very anxious or depressed	4.0% (2)	5.3% (3)	4.5% (3)	4.9% (2)	2.4% (1)	6.1% (4)	4.4% (2)	4.8% (3)
Health status	Better	10.8% (4)	7.5% (3)	8.7% (4)	9.7% (3)	12.0% (3)	7.7% (4)	18.8% (6)	2.2% (1)
	Same	29.7% (11)	17.5% (7)	30.4% (14)	12.9% (4)	24.0% (6)	23.1% (12)	28.1% (9)	20.0% (9)
	Worse	59.5% (22)	75.0% (30)	60.9% (28)	77.4% (24)	64.0% (16)	69.2% (36)	53.1% (17)	77.8% (35)

In parentheses: number of patients.

that a poorest quality of life has a negative impact on addressing the treatment process.

The results of this study highlight the negative impact of toxicities such as nausea, dysgeusia, peripheral neuropathy, loss of appetite, myalgia, and peripheral edema on breast cancer

patients' quality of life. As García-Luna et al<sup>[33]</sup> show, nausea, dysgeusia, and loss of appetite induce the onset of malnutrition in the cancer patient. This leads to a decrease in muscle mass and, therefore, favors overall weakness of the patient. Its impact implies, in addition to decreasing quality of life (data

**Table 6****Distribution of the different indicators of health-related quality of life based on eye toxicity indicators.**

		Conjunctivitis	
		No	Yes
Mobility	I have no problems walking	78.8% (52)	65.1% (28)
	I have some problems walking	18.2% (12)	32.6% (14)
	I have to stay in bed	3.0% (2)	2.3% (1)
Personal care	I have no problems with personal care	95.5% (63)	95.2% (40)
	I have some problems washing myself and getting dressed	4.5% (3)	4.8% (2)
	I cannot wash myself or get dressed	0.0% (0)	0.0% (0)
Daily activities	I have no problems performing my daily activities	54.5% (36)	51.2% (22)
	I have some problems performing my daily activities	45.5% (30)	46.5% (20)
	I cannot perform my daily activities	0.0% (0)	2.3% (1)
Pain/discomfort	I have no pain or discomfort	43.9% (29)	32.6% (14)
	I have moderate pain or discomfort	53.0% (35)	62.8% (27)
	I have a lot of pain or discomfort	3.0% (2)	4.7% (2)
Anxiety/depression	I am not anxious or depressed	62.1% (41)	66.7% (28)
	I am moderately anxious or depressed	33.3% (22)	28.6% (12)
	I am very anxious or depressed	4.5% (3)	4.8% (2)
Health status	Better	10.4% (5)	6.7% (2)
	Same	29.2% (14)	13.3% (4)
	Worse	60.4% (29)	80.0% (24)

In parentheses: number of patients.

**Table 7****Distribution of the different indicators of health-related quality of life based on constitutional symptom indicators.**

		Asthenia	
		No	Yes
Mobility	I have no problems walking	87.5% (14)	70.7% (65)
	I have some problems walking	0.0% (0)	28.3% (26)
	I have to stay in bed	12.5% (2)	1.1% (1)
Personal care	I have no problems with personal care	100.0% (13)	94.5% (86)
	I have some problems washing myself and getting dressed	0.0% (0)	5.5% (5)
	I cannot wash myself or get dressed	0.0% (0)	0.0% (0)
Daily activities	I have no problems performing my daily activities	81.3% (13)	47.8% (44)
	I have some problems performing my daily activities	18.8% (3)	51.1% (47)
	I cannot perform my daily activities	0.0% (0)	1.1% (1)
Pain/discomfort	I have no pain or discomfort	68.8% (11)	34.8% (32)
	I have moderate pain or discomfort	31.3% (5)	60.9% (56)
	I have a lot of pain or discomfort	0.0% (0)	4.3% (4)
Anxiety/depression	I am not anxious or depressed	75.0% (12)	61.5% (56)
	I am moderately anxious or depressed	25.0% (4)	33.0% (30)
	I am very anxious or depressed	0.0% (0)	5.5% (5)
Health status	Better	0.0% (0)	10.1% (7)
	Same	37.5% (3)	21.7% (15)
	Worse	62.5% (5)	68.1% (47)

In parentheses: number of patients.

corroborated in this study), an increase in dependence on care by family members or caregivers and an increased state of immunosuppression, which is associated with the risk of infectious complications. It is reasonable to conclude that all of this will psychologically affect the cancer patient.

Furthermore, it is noteworthy that 89.9% of patients deny having suffered an episode of vomiting and that 75.2% of them have not suffered peripheral edema during the last 21 days. However, vomiting is commonly reported as associated with these chemotherapy treatments.<sup>[9]</sup> The low incidence of vomiting referred to in this study may be due to the high efficacy of the used prophylactic antiemetic: aprepitant.<sup>[34,35]</sup> However, treatment

with aprepitant does not reduce nausea, something that is confirmed by 67.0% of patients in this study who claim to have suffered it. Likewise, the prophylactic use of corticosteroids may be associated with the low percentage of peripheral edema reported.

In addition, other toxicities such as mucositis, headache, abdominal pain, arthralgia, conjunctivitis, and asthenia showed a negative trend on the patients' quality of life, so it could be expected that, by increasing the sample size, this trend would become clearer and statistically significant.

Likewise, this study demonstrates the negative implication of the different toxicities on each of the health-related quality-of-life

**Table 8****Distribution of the different indicators of health-related quality of life based on lymphatic system toxicity indicators.**

		Peripheral edema	
		No	Yes
Mobility	I have no problems walking	82.7% (67)	44.4% (12)
	I have some problems walking	13.6% (11)	55.6% (15)
	I have to stay in bed	3.7% (3)	0.0% (0)
Personal care	I have no problems with personal care	97.5% (79)	88.5% (23)
	I have some problems washing myself and getting dressed	2.5% (2)	11.5% (3)
	I cannot wash myself or get dressed	0.0% (0)	0.0% (0)
Daily activities	I have no problems performing my daily activities	58.0% (47)	37.0% (10)
	I have some problems performing my daily activities	42.0% (34)	59.3% (16)
	I cannot perform my daily activities	0.0% (0)	3.7% (1)
Pain/discomfort	I have no pain or discomfort	48.1% (39)	14.8% (4)
	I have moderate pain or discomfort	49.4% (40)	77.8% (21)
	I have a lot of pain or discomfort	2.5% (2)	7.4% (2)
Anxiety/depression	I am not anxious or depressed	69.1% (56)	46.2% (12)
	I am moderately anxious or depressed	25.9% (21)	50.0% (13)
	I am very anxious or depressed	4.9% (4)	3.8% (1)
Health status	Better	11.5% (6)	4.0% (1)
	Same	30.8% (16)	8.0% (2)
	Worse	57.7% (30)	88.0% (22)

In parentheses: number of patients.



**Table 9**  
**Correlation between adverse reactions and health-related quality of life.**

Adverse reaction	Mann-Whitney <i>U</i> test	<i>P</i>	Cohen <i>d</i>
Vomiting	267 (77)	.879	0.13
Nausea	440 (77)	.020*	0.56
Diarrhea	746 (78)	.923	0.03
Constipation	613 (76)	.522	0.17
Mucositis	548 (77)	.081	0.46
Loss of appetite	455 (78)	.002*	0.77
Dysgeusia	107 (78)	.038*	0.89
Skin reaction in hands and/or feet	510 (77)	.626	0.09
Impaired nails	564 (77)	.642	0.14
Skin allergies	213 (76)	.014	0.88
Peripheral neuropathy	185 (77)	.000*	1.34
Myalgia	628 (77)	.248	0.30
Abdominal pain	559 (77)	.104	0.37
Joint pain	502 (77)	.103	0.39
Muscle pain	436 (77)	.003*	0.76
Conjunctivitis	581 (78)	.148	0.35
Asthenia	168 (77)	.068	0.64
Peripheral edema	337 (77)	.001*	0.88

\* Statistically significant.

indicators. Focusing on each of the quality-of-life variables, there are differences in the involvement of certain toxicities in the different components.

On the one hand, the anxiety or depression indicator remains affected by nausea, mucositis, peripheral neuropathy, and abdominal pain. As regards pain or discomfort, 7 toxicities would be involved: loss of appetite, dysgeusia, peripheral neuropathy, arthralgia, myalgia, asthenia, and peripheral edema.

Daily activities are influenced by loss of appetite, peripheral neuropathy, and asthenia. This last toxicity also has an impact on the mobility indicator, in addition to peripheral edema. Personal care is only affected by peripheral neuropathy.

In the case of peripheral neuropathy and peripheral edema, it is noteworthy that despite obtaining a below 25% percentage of presence in the study patients, these are toxicities that significantly affect quality of life. This may be due to the lack of validity of all the symptoms associated with these variables.<sup>[6]</sup> Peripheral neuropathy is also worth noting because it is the toxicity that affects a greater number of quality-of-life indicators (anxiety or depression, pain or discomfort, daily activities, and personal care). This may be due to the severity of this toxicity as it affects the whole organism, from deep pain followed by numbness, mainly in the hands and feet, muscle involvement with a feeling of weakness, as well as problems with digesting, sexual relationships, heart involvement, and more.

Beusterien et al.<sup>[18]</sup> demonstrated in their study that breast cancer patients prioritized certain side effects, such as peripheral neuropathy, over others, such as alopecia, which they considered minor. They even claimed to be willing to accept a less convenient chemotherapy treatment scheme to avoid an increased risk of side effects such as peripheral neuropathy.

In short, despite the advances in the control of symptoms associated with chemotherapy treatments, the patient's perception is still a pending task for all health workers. These must be aware of the importance of knowing the patient and thus avoiding hospital admissions, delays in chemotherapy cycles, or

even suspension of the cycles as a result of accumulated toxicity.<sup>[11,14]</sup>

As for the limitations of this study, as a 1-center study, there is a possibility that the study population will be subjected to certain common bias. In addition, the questionnaire was carried out randomly in a specific cycle of the 6 corresponding to the complete treatment of the patient, so there is a possibility that the studied cycle was not the one in which the patient presented a higher number of toxicities. Similarly, as an observational design, causal relationships cannot be established, and we can only talk of correlations between the variables. Therefore, further studies with a larger sample size would be needed to corroborate the results and conclusions of this study.

In general, quality-of-life results highlight the need to improve the assessment of the effects of the treatment on the patients' quality of life. This could be the goal of developing a self-refillable questionnaire regarding the patients' perception of their own health status and symptoms to obtain more information and more detailed data on these issues through patient self-assessment. Patients could bring this self-assessment home or have a digital record available with the aim of obtaining more complete data on the adverse reactions suffered during the 21 days the patient is at home. In this line, there are studies<sup>[9,34]</sup> that have analyzed the perceived quality of life of patients as compared with the usual practice, which show that quality of life is affected by the care received in hospitals during the patient's illness, thus highlighting the lack of information that health professionals have about patients' perceptions.

The importance of introducing a multidisciplinary team aimed at improving the acceptance of chemotherapy in these patients has been demonstrated in a cohort study conducted among 13,722 breast cancer patients.<sup>[36]</sup> This is why this could be a line of improvement in real care for these types of cancer patients.

On the other hand, it would be necessary to raise awareness among healthcare professionals of the importance of adverse reactions in chemotherapeutic treatments. Cancer patients may feel more welcomed by the health system and more participative in everything that affects the evolution of their treatment and disease.<sup>[11]</sup>

In conclusion, the presence of adverse reactions related to the TEC treatment scheme significantly decreases health-related quality of life. In particular, nausea, loss of appetite, dysgeusia, peripheral neuropathy, myalgia, and peripheral edema are those toxicities where this difference has been significant.

## Author contributions

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