Adverse events from systemic treatment of cancer and patient-reported quality of life

Vicente Valentí, PhD, a Javier Ramos, MD, a Cristina Pérez, MD, a Laia Capdevila, MD, b Lidia Tikhomirova, MD, c Javier Márquez, MD, c Meritxell Mas, MD, c Carme Nolla, MD, d Josep Bitria, MD, d Isabel Bevià, MD, d Belén Pérez, MD, d Albert Josa, MD, d Judit Montoya, MD, d Eugenia Sopena, MD, a and José-Luis Pinto-Prades, PhD e

a Medical Oncology, Hospital Santa Tecla, b Medical Oncology, Hospital Comarcal del Baix Penedès, c Internal Medicine, Hospital Santa Tecla, and d Primary Health Care Center-Llevant, all in Tarragona, Spain; e Health Economics, Universidad de Navarra, Campus Universitario Pamplona, Navarra, Spain; and f Health Economics Department, Glasgow Caledonian University, Glasgow, United Kingdom

Background Treatment-related adverse events (AEs) have a negative impact on the quality of life (QoL) of cancer patients. Patient and general public views can help in the investigation of patient needs and preferences.

Objective To compare the impact on QoL reported by cancer patients who have experienced a particular AE with that envisioned by general public participants (hypothetical patients) who have not experienced AEs.

Methods Five AEs were selected: total alopecia (Common Terminology Criteria for Adverse Events [CTCAE] grade 2), acneiform rash (CTCAE, grade 1 and grades 2-4), oxaliplatin-associated peripheral neuropathy (oxaliplatin-specific scale, grades 1, 2, and 4); diarrhea and vomiting (CTCAE, grades 1-2 and grades 3-4), resulting in 10 toxicity variables. Cancer patients and general public participants completed the Visual Analog Scale (VAS; 0 = poorest QoL; 100 = better QoL), and cancer patients also completed the EQ-5D-5L questionnaire (full range for Spanish population, -0.654-1.000).

Results 246 general public participants and 200 toxic events in 139 cancer patients were analyzed. For all 10 endpoints, the mean VAS was higher for patients than for the general public participants. That difference was statistically significant (Mann-Whitney U test) for all endpoints except for grade 1 neuropathy and grade 1 rash. For both groups, alopecia had a lower impact on quality of life than did severe rash (mean VAS for patients, 77 [alopecia] vs 59 [rash], compared with 55 vs 47, respectively, for the general public group). There was a positive linear correlation between the EQ-5D-5L and VAS (Spearman rho, 0.681; P = .001).

Limitations Patients were asked to score AEs as separate and encapsulated from other concurrent symptoms. This exercise may be rather difficult for patients.

Conclusions The impact of therapy-related AEs on QoL was lower in patients who have experienced the AEs than it was for the general public participants who had not experienced the AEs. The EQ-5D-5L is a useful tool for evaluating AEs.

Funding/sponsorship Provided by the Oncologic Association Dr Amadeu Pelegrí (AODAP), a charitable organization led by cancer patients and based in Salou, Spain.
observed between actual patients and the general public. It is not clear if it reflects the inability of members of the general public to fully grasp the relative severity of health problems or to the adaptation process of patients. This fact may obscure a negative impact on QoL which, in turn, could be detected using the general public as a surrogate. This debate is prolonging in time and it is far from over. 8,9

Based on this background, this study investigates the impact of AEs on QoL of cancer patients from the perspective of cancer patients who had experienced the AEs of interest (ex post population) and the perspective of members of the general public. The second group comprised participants imagining themselves as hypothetical cancer patients experiencing the AEs (ex ante population). Previous studies with this dual approach allowing for comparisons between these two populations are small or centered on a few AEs.10 Therefore, a large and comprehensive study on the impact of AEs on QoL is lacking. Supported by previous literature, the investigational hypothesis was that ex post impact would be significantly lower than that imagined in an ex ante setting. The secondary objective is to study the potential use of the EuroQol (EQ-5D) instrument for health-related QoL in the measurement of the impact of AEs in cancer patients. This generic instrument is based on interviews with members of the general public. We tried to investigate to what extent those values relate to the cancer patients’ evaluation of their own health during treatment. The ultimate goal of the study is to assist in increasing the utility that patients derive from the benefits associated with cancer treatment.

Methods

Selection of AEs

Five AEs related to systemic treatment of cancer – alopecia, acneiform rash, oxaliplatin-associated peripheral neuropathy, diarrhea, and vomiting – were selected for the study. Investigators set up different relevant cut-off points for severity, resulting in 10 toxic events that were ad hoc defined as the variables for the study (Table 1). We used the Common Terminology Criteria for Adverse Events (CTCAE, version 4) to classify alopecia, acneiform rash, diarrhea, and vomiting. For oxaliplatin-associated peripheral neuropathy, we adapted Misset’s oxaliplatin-specific scale11 (range, grade 1-4; Table 1) in which grade 1 (neurotoxicity [NTX] 1) = paresthesias only with cold; a few days; grade 2 [NTX2] = paresthesias with and without cold; permanent may last months; and grade 4 [NTX3] = paresthesias with motor impairment; permanent may last months.

Participants

Two populations were included in the study: cancer patients who had experienced a particular AE and received treatment at the medical oncology departments of Hospital Santa Tecla and Hospital del Vendrell in Tarragona, Spain; and participants from the general public who received care at the Primary Health Care Center-Llevant in the same city.

Cancer patients. These participants had to be 18 years...
or older and had to have experienced 1 of the 10 toxic
events in the 5 years before inclusion in the study; the
treatment setting could be either curative attempt (adju-
vant, neoadjuvant) or palliative, and patients with ongoing
treatment should have received almost 3 months of treat-
ment. Patients were excluded if they had an ECOG PS
grade of 3 or more (Eastern Cooperative Oncology Group
Performance Status; range, 0-5, where 0 = fully active, 3 =
capable of limited self-care; confined to bed or chair
more than 50% of waking hours, and 5 = dead). A particu-
lar patient with cancer could be included because of more
than 1 study toxic event (eg, alopecia and severe vomiting
or NTX1 and NTX2) but had to complete separate ques-
tionnaires for the different toxic events.

General public group. Participants in this group were
selected from the records of general practitioner consul-
tations at the aforementioned primary health care center.
They had to be 18 years or older and could not have a
history of cancer or symptomatic/severe chronic diseases (eg,
they could have hypertension or diabetes without chronic
target organ involvement, or they could be patients with
either acute nonserious illness or nonserious injuries).

Survey procedures
Cancer patients. Participants in this group filled in 2 ques-
tionnaires provided by a medical oncologist in a face-to-face
interview: the 5-dimension, 5-level EuroQol (EQ-5D-5L)
questionnaire in reference to the days when patients were
suffering the toxic event; and a visual analog scale (VAS)
answering the question: How do you feel that this AE has
impacted on your QoL the days you have experienced it?
VAS scores ranged from 0 (the poorest QoL, the high-
est impact) to 100 (the better QoL, the lower impact). The
EQ-5D-5L has 5 dimensions (Mobility, Self-care, Daily
life activities/social performance, Discomfort/pain, and
Anxiety/depression) with 5 level response options each (No
problem at all, Light problem, Moderate problem, Severe
problem, Extreme problem/unable).12 The combination of
5 answers is converted to a single score, which is different
for different countries; in the validated version for Spanish
population, the score ranges from -0.654 (the worst health
state) to 1.000 (the best health state). Patients were asked
to make an effort to separate and encapsulate the impact of
eye every adverse event and separate it from others they may
have experienced during the same period. Table 2 summa-
rizes survey procedures.

General public group. Two internal medicine residents
who administered the questionnaire to the participants
of the public group were well trained to carefully explain
what each of the 10 the toxic events meant. Some details
on these explanations are shown in Table 1, and the full
set of explanations is shown in Appendix 1 (online only).
Participants in the general public group were asked in a
face-to-face interview to imagine they were cancer patients
and envision how these toxic events would impact on their
QoL if they were undergoing systemic treatment of cancer.
They were asked to rate the imagined impact with the VAS
(1 VAS/every toxic event = 10 VAS/participant). Then, they
were presented with 10 cards, each with the name of 1 of
the 10 toxic events (Appendix 2 [online only]), to show
them the order of the impact on QoL based on their scores
(respecting ties). The participants were asked if they agreed
with the order, and if they did not, they were invited to
change the scores. Therefore, results in the general public
group also show the rank-order of the study toxic events.

Statistical analysis
We calculated the sample size as follows:
- For the population of patients with cancer, we estimated
  that 800 patients a year start chemotherapy in our medi-

<table>
<thead>
<tr>
<th>Study population</th>
<th>VAS</th>
<th>EQ-5D-5L</th>
<th>Rank order</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cancer patients</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td></td>
<td>Only toward the toxic event that patient has experienced (1 VAS per toxic event)*</td>
<td>Only toward the toxic event that patient has experienced 20 each toxic event</td>
<td></td>
</tr>
<tr>
<td>General public</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td></td>
<td>One per every one of the 10 toxicity variables</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>One per toxic event in patients with cancer</td>
<td>One per toxic event in patients with cancer</td>
<td>One ordination by each general population participant</td>
</tr>
</tbody>
</table>

EQ-5D-5L, 5-level EuroQol-5D version; VAS, visual analog scale
\*Some patients may have been included for more than one toxic event and they filled both one VAS and one EQ-5D-5L per toxic event.
cal oncology department, therefore, with a 6% precision, we needed 182 toxic events evaluated. We decided that to cover 10% losses, we would need to include 20 cases for every 1 of the 10 toxic events.

For the general public, for representativeness for 75,000 inhabitants who live in the area serviced by the health care center, with 6% precision, we needed 240 participants; with 2% expected losses, 249 participants were to be enrolled.

Primary outcomes were VAS score in cancer patients and VAS score in the general public. Primary analyses were comparison between VAS in both populations. Secondary outcomes were EQ-5D-5L score in cancer patients, and intra-participant rank-order in the general public group. Secondary analyses were correlation between VAS score and EQ-5D-5L in cancer patients and descriptive analysis of rank-ordered data in the general public group.

It was planned to compare means of quantitative variables with the Mann-Whitney U test and to assess correlation between quantitative variables with the Spearman rho test. All tests for contrast were nonparametric because a normal distribution was not expected from quoted scores with some ceiling or floor effect. A hierarchical generalized cluster analysis was planned to study clusters of variables grouped by VAS score in the public group.

Ethics
The study was conducted in accordance with the Declaration of Helsinki version Fortaleza 2013 and was approved by the institutional review board of the participant institutions. All of the patients provided written informed consent before study entry. Data of the participants of the general public were anonymous, so those participants were asked to provide only oral assent, with the permission of the review board.

Results
Between December 1, 2013 and January 31, 2015, a total of 250 participants of the general public and 139 cancer patients were included in the study. Four participants of the general public had incompletely filled the questionnaire and were excluded from the study, resulting in 246 participants with complete data available. There were no losses in the patient group, of whom 79 (57%) were currently on treatment and 118 (85%) had received the treatment in the previous 2 years. The total number of study toxic events in the 139 cancer patients was 200 (20 by each of the 10 study toxicity variables). Of those, 42 patients (30%) experienced (and were included in the study for) more than 1 toxic event.

Of the 139 patients, 91 (65%) received the treatment with curative intent. The most frequent diagnosis was colorectal cancer in 77 patients (55%), followed by breast cancer (13 patients, 9.4%), and lung cancer (11 patients, 7.9%). Systemic treatment of cancer was one of these options:

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>No. of patients/participants, n (%)</th>
<th>Cancer patients</th>
<th>General population</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>(n = 139)</td>
<td>(n = 246)</td>
</tr>
<tr>
<td>Median age, y (range)</td>
<td>64 [23-84]</td>
<td>49 [18-92]</td>
<td></td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>83 [60]</td>
<td>135 [55]</td>
<td></td>
</tr>
<tr>
<td>Women</td>
<td>56 [40]</td>
<td>111 [45]</td>
<td></td>
</tr>
<tr>
<td>Treatment intention</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Curative</td>
<td>91 [65]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Palliative</td>
<td>48 [34]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tumor site</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Colorectal</td>
<td>77 [55]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Breast</td>
<td>13 [9-4]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lung</td>
<td>11 [8]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stomach</td>
<td>7 [5]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pancreas</td>
<td>4 [3]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Larynx</td>
<td>4 [3]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Testicular germ-cell</td>
<td>4 [3]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Uterine sarcoma</td>
<td>4 [3]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bladder</td>
<td>3 [2]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>12 [9]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chemotherapy regimens</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>mFOLFOX6</td>
<td>51 [37]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alone</td>
<td>35 [25]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Combination</td>
<td>16 [12]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Xelox</td>
<td>10 [7]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alone</td>
<td>9 [6]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Combination</td>
<td>1 [1]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anti-EGFR containing</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cetuximab</td>
<td>22 [16]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Panitumumab</td>
<td>15 [11]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Erlotinib</td>
<td>4 [3]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Afatinib</td>
<td>2 [1]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anthracyclin-based</td>
<td>14 [10]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Platinum-based</td>
<td>19 [14]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cisplatin</td>
<td>14 [10]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Carboplatin</td>
<td>5 [4]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Irinotecan-containing</td>
<td>18 [13]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Taxane-containing</td>
<td>12 [8]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bevacizumab-containing</td>
<td>13 [9]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of toxic events</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>97 [67]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>30 [21]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>9 [7]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>3 [2]</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

EGFR, epidermal growth factor receptor; mFOLFOX6, modified folinic acid (leucovorin calcium), fluorouracil, and oxaliplatin

- Calculations on all these baseline characteristics in the group of cancer patients were also performed on the basis of toxic events (N = 200). Median age then was 63 years (instead of 64) and percentage differences between these 2 sets were less than 3% (data not shown).

TABLE 3 Baseline characteristics

Valenti et al
chemotherapy alone, anti-EGFR [epidermal growth factor receptor] alone, chemotherapy plus anti-EGFR, or chemotherapy plus other biologics. The chemotherapy regimen most frequently administered was mFOLFOX6 [modified leucovorin calcium (folinic acid), fluorouracil, and oxaliplatin] which, alone or in combination, was administered to 51 patients (37%). An anti-EGFR agent was administered to 22 patients (16%): cetuximab (15 patients), panitumumab (4 patients), erlotinib (2 patients) and afatinib (1 patient). The baseline characteristics of the patients and participants in the study are shown in Table 3.

For all 10 toxicity outcomes, the mean VAS score from the general public was numerically lower (lower QoL, more impact) than that resulted from the cancer patients who had actually experienced the toxic event of interest (Table 4 and Figure). Taking off 2 mild effects (NTX1 and mild rash), for the 8 remaining toxic events, this difference was statistically significant (Mann-Whitney U test; \( P < .01 \) for severe vomiting, severe diarrhea, and alopecia; \( P < .001 \) for NTX2, NTX3 and mild diarrhea; \( P = .03 \) for severe rash; \( P = .04 \) for mild vomiting). Severe vomiting resulted in the worst VAS score for cancer patients (median VAS, $34$) and NTX3 had the worst VAS score for the general public participants (median, VAS $19$). Table 4 summarizes the 4 sets of results (patient and general public VAS and quality of life scores).

Regarding the results of the esthetic toxicities compared with each other, impact from severe rash was considered higher than that from alopecia for both populations, patients (mean VAS, $59$ [rash] vs $77$ [alopecia]; mean EQ-5D-5L score, $0.725$ [rash] vs $0.921$ [alopecia]) and the general public (mean VAS, $47$ vs $55$; EQ-5D-5L, rank order $5$ vs $9$). In the group of patients, linear correlation between VAS and EQ-5D-5L score was assessed resulting in a significant positive correlation (Spearman \( P = .001 \) with a correlation coefficient Rho $0.681$ (Appendix 3 [online only]). Also, a positive linear correlation was observed between the 10 means of the cancer patients’ VAS and the 10 means of the general public patient and general public VAS.

### Table 4 Primary analysis

<table>
<thead>
<tr>
<th>Toxic event</th>
<th>VAS mean</th>
<th>General public (rank order)*</th>
<th>Patients (rank order)*</th>
<th>Change in means</th>
<th>Mann-Whitney U test</th>
<th>EQ-SD-5L mean score (rank order)*</th>
<th>General public rank ordered*</th>
<th>Patients VAS and EQ-SD-5L</th>
<th>Median patient and general public VAS</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Severe vomiting</td>
<td>20 (2)</td>
<td>34 (1)</td>
<td>+14</td>
<td>( P &lt; .01 )</td>
<td>0.537 (2)</td>
<td>1 (1)</td>
<td></td>
<td></td>
<td>Spearman ( P = .001 ) Rho: 0.681</td>
</tr>
<tr>
<td>2. Severe diarrhea</td>
<td>25 (3)</td>
<td>39 (2)</td>
<td>+14</td>
<td>( P &lt; .01 )</td>
<td>0.516 (1)</td>
<td>3 (3)</td>
<td></td>
<td></td>
<td>Spearman ( P = .001 ) Rho: 0.879</td>
</tr>
<tr>
<td>3. NTX3</td>
<td>19 (1)</td>
<td>54 (3)</td>
<td>+35</td>
<td>( P &lt; .001 )</td>
<td>0.554 (3)</td>
<td>1 (1)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4. Severe rash</td>
<td>47 (5)</td>
<td>59 (4)</td>
<td>+12</td>
<td>( P = .03 )</td>
<td>0.725 (4)</td>
<td>7 (5)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5. Mild vomiting</td>
<td>49 (6)</td>
<td>61 (5)</td>
<td>+12</td>
<td>( P = .04 )</td>
<td>0.746 (6)</td>
<td>8 (6)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6. NTX2</td>
<td>43 (4)</td>
<td>71 (6)</td>
<td>+28</td>
<td>( P &lt; .001 )</td>
<td>0.775 (5)</td>
<td>5 (4)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>7. NTX1</td>
<td>72 (9)</td>
<td>75 (7)</td>
<td>+3</td>
<td>NS</td>
<td>0.877 (9)</td>
<td>9 (8)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>8. Alopecia</td>
<td>55 (8)</td>
<td>77 (8)</td>
<td>+22</td>
<td>( P &lt; .01 )</td>
<td>0.921 (10)</td>
<td>9 (9)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>9. Mild diarrhea</td>
<td>51 (7)</td>
<td>78 (9)</td>
<td>+27</td>
<td>( P &lt; .001 )</td>
<td>0.867 (8)</td>
<td>7 (6)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>10. Mild rash</td>
<td>80 (10)</td>
<td>84 (10)</td>
<td>+4</td>
<td>NS</td>
<td>0.866 (7)</td>
<td>10 (10)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

EQ-5D-5L, 5-level EuroQol-5D version; NS, not significant; NTX, neurotoxicity; VAS, visual analog scale.

*Rank order among the 10 toxic events in the columns of this table. Rank order results among the 10 toxic events scored ordered by each member of public, with 1 = the worst and 10 = the best.

**TABLE 4 Primary analysis**

**FIGURE** Patient and general public participant visual analog scale*

NTX, neurotoxicity; VAS, visual analog scale.

*Except for NTX1 and Mild Rash, all P-values for the patient vs general public participant comparisons are statistically significant (Mann-Whitney test).
lic participants’ VAS (Spearman *P* = .001; coefficient Rho 0.879). Both ceiling and floor effect were observed for VAS in the 2 populations, but only ceiling effect for EQ-5D-5L in the patient population. The most important floor effect was for NTX3, with 66 participants (27%) of the general public group scoring VAS 0 (see Appendix 4 [online only] for the frequencies of answers for every level of the 5 dimensions of the EQ-5D-5L). An analysis of the results, considered as an intraparticipant rank-ordered evaluation, was performed in the general public group. Fourteen participants of that group (5.7%) changed their scores after they were presented with the order shown in cards. Mode of the ranks show that NTX3 and severe vomiting were the worst-scored toxic events. The most frequent rank-order for alopecia and severe rash were (from best to worst) the second and the fourth, respectively.

### Discussion

The findings in this study show that impact on QoL imagined by members of the general public is higher than that declared by cancer patients who have experienced the AEs. It is worth noting that that result was observed for all 10 toxic events, thus confirming the initial hypothesis of the study. However, the graph shows a strong parallel between the 2 groups, which means that both populations similarly perceive upward and downward variations in the impact resulting from the different toxic events (Figure).

Three previous studies have addressed the comparison of the impact of different AEs in these 2 populations and findings from all 3 showed the same systematic difference between patients and the general public participants. The first, Calhoun and colleagues used time to trade-off (TTO, a measure of the QoL a person or groups is experiencing) to compare therapies for ovarian cancer in patients and the general population (*n* = 39 for each group). The results showed that cancer patients valued more the health status associated with toxicity than did the general public participants. The design of the second study, by Havrilesky and colleagues, was similar to that of the present study, and they compared toxic events one by one, using VAS and TTO in 13 ovarian cancer patients and 37 women of the general public. The investigators found the same results as we did on the parallel of the 2 groups and also a very similar order of the toxic events. Indeed, alopecia was the less bothersome, whereas both motor neuropathy and severe vomiting were among the worst toxic events. Therefore, our results correlate perfectly with theirs. Best and colleagues found that health states values associated with oxaliplatin-related peripheral neuropathy were lower in the general public population compared with those of cancer patients. Besides adaptive behavior of the patients, all these results may be explained by an established awareness cancer patients have of the dual outcome of cancer treatments (AEs and benefits from the treatment). This awareness is absent in the general public participants, who can only envision the negative outcomes and who do not realize the importance of the benefits. Findings from previous studies conducted in several tumor types such as breast cancer, non-small-cell lung cancer, thyroid cancer, and renal cancer have shown that patients are willing to trade-off AEs for treatment benefits.

Alopecia has been considered as one of the most distressing and troublesome AEs of cancer therapy. However, in the present study, alopecia was rated inside the range of mild toxic events as it is in the study by Havrilesky and colleagues. Our results show that alopecia was placed as the first less damaging toxic event when assessed with the EQ-5D-5L, the second less damaging when assessed with a rank-order system, and the third less damaging when assessed the VAS. This could be related to current fashion trends that promote shaving one’s hair, which minimizes the social stigma of alopecia and its association with cancer treatment.

The other esthetic event we analyzed was acneiform rash associated with anti-EGFR agents. Our results show that severe rash was rated as clearly worse than alopecia by the 2 populations, irrespective of the measuring instrument (VAS, EQ-5D-5L, or ordinal assessment). To our knowledge, the present study is the first to demonstrate the relative impact of total alopecia and severe rash on patient QoL. This result is even more significant considering that we included grade 2 acneiform rash inside the Severe Rash toxic event. Our results show that the worst AEs for both populations were severe vomiting and neurotoxicity with functional impairment. The high impact of severe vomiting, the quintessentially chemotherapy-induced AE, was to be expected because it is strongly supported by a number of previous reports, as is also true for peripheral motor neuropathy.

EQ-5D is a powerful instrument for measuring health status and is widely used to describe and evaluate patient health. Our results from the 5 dimensions represented by a single score were well correlated with the results of the VAS. However, whereas median VAS scores were evenly distributed in the 0–100 range of the VAS, median EQ-5D-5L scores were distributed mainly in the 0.5–1.0 range (full range, -0.654–1.000, for Spanish population). The final single score of the original EQ-5D is based on responses from the general public, and we have shown that its use is a valid option when the objective is the evaluation of AEs in patients with cancer. Management of AEs is of the utmost importance in this era of personalized cancer medicine. Basch and colleagues recently reported that an intensive web-based follow-up of AEs during chemotherapy improved overall survival compared with standard follow-up. The results of our study show that patients have strongly defined preferences regarding AEs. Therefore, therapeutic strategies with a personalized approach in managing AEs would be associated with increased effectiveness.
There are some limitations in the present study. First, we modified slightly the EQ-5D-5L questionnaire by asking patients to recall and rate the days they experienced the adverse event instead of asking for "today's feelings." It is not known how this modification affects internal validity of this study. Second, we asked patients to isolate the toxic event to rate it independently from the other toxic events. We believe that this request may have been difficult for some patients to do because they might have experienced more than 1 toxic event concurrently. Third, using VAS to assess health status may be a weakness because it has been considered to be too straightforward an instrument. Likewise, there are some strengths of the study: it was performed in a face-to-face manner; it displayed cardinal and ordinal results for participants in the public group; and the results are the same as those in a previous study.14

In conclusion, patients with cancer who have experienced AEs perceive a lower impact on their QoL compared with that envisioned by participants from the general public. The EQ-5D-5L is a useful tool for evaluating cancer-therapy–related AEs. The impact of alopecia on QoL was notably low and even lower than that of severe rash. Further investigation on this issue should focus on patients' and oncologists' shared choices, which increasingly will be driven by patient preferences.

Acknowledgment
The Oncologic Association Dr Amadeu Pelegrí (AODAP), a charitable organization led by cancer patients and based in Salou, Spain, provided the financial support needed to conduct this study (www.aodapelegri.com).

References