Evaluation of Scores to Reflect Toxicity Impact on Quality of Life of Patients With Platinum-Resistant Ovarian Cancer: AURELIA Substudy

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ABSTRACT

Background: Current standards for toxicity reporting do not fully capture the impact of adverse events (AEs) on patients' quality of life (QoL). This study aimed to evaluate the association between toxicity and QoL by using toxicity scores that take into account CTCAE grade grouping and AE duration and cumulation. **Methods:** Analyses were performed on the AURELIA trial dataset, including 361 patients with platinum-resistant ovarian cancer treated with chemotherapy alone or with bevacizumab. Global and physical functioning QoL were issued from the EORTC QoL Questionnaire-Core 30 (QLQ-C30), collected at baseline and 8/9 and 16/18 weeks after treatment initiation. Four toxicity scores were computed: the total number of AEs, multiplied by their grade and not, and the cumulative duration of AEs, weighted by their grade and not. Each score included all AEs or only grade 3/4 nonlaboratory or treatment-related AEs. The relationship between toxicity scores and QoL was assessed through linear mixed regression. **Results:** We found that 171 (47.5%) and 43 (11.9%) patients experienced at least one grade 3 or 4 AE, respectively, whereas 113 (31.4%) experienced grade 2 AEs only. Physical QoL was negatively associated with all toxicity scores when computed with all grades of AEs (all $P<.01$), with a weaker association when treatment-related AEs were considered. Global QoL was negatively associated with toxicity scores computed with nonlaboratory all-grade AEs only (β, –3.42 to –3.13; all $P<.01$). Degrees of association were lower when considering the AE duration. **Conclusions:** In this analysis of patients with platinum-resistant ovarian cancer, toxicity scores based on the cumulative number of AEs, modulated or not by grade, were more effective at predicting QoL changes than those based on AE duration. Toxicity impact on QoL was better reflected when grade 2 AEs were taken into account together with grade 3/4 AEs, whatever their treatment imputability, and when laboratory AEs were excluded.

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Background

In palliative oncology practice, the benefit/risk balance is iteratively assessed to decide the more beneficial and acceptable treatment for patients. Anticipated effects of treatments on patients' quality of life (QoL) are highly weighted in the benefit/risk assessment process. Platinum-resistant ovarian cancer (PROC) is a palliative situation with a poor prognosis. The disease causes a plethora of symptoms that impact patients' QoL.[1] Therefore, the main goal of treatment is to improve progression-free survival (PFS) and alleviate any preexisting tumor-related symptoms with limited toxicity or negative impact on QoL.

Although the evaluation of efficacy is standardized in randomized phase III clinical trials with well-defined endpoints, evaluation of the tolerance to treatments and its impact on QoL remains more challenging. Recent efforts were made to improve the reporting of adverse events (AEs) by standardizing the terminology through the MedDRA terminology and the severity grading system through the NCI's CTCAE. AE data are usually reported through frequency tables of the highest-grade AEs.[2] Such presentation allows a synthetic overview of

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the safety profile of drugs, with a focus on high-grade AEs that may induce treatment interruption or dose reduction. However, major data are still lacking to evaluate the impact of AEs on patients' QoL, such as evolution over time (duration, recurrence, severity), cumulative toxicity, and description of low-grade AEs, which is of interest in highly symptomatic patients such as those with PROC.[3,4]

Novel approaches have been developed to thoroughly summarize AE burden by constructing novel toxicity scores. Carbini et al[5] proposed the weighted toxicity score, defined as the sum of the proportion of patients with toxicities weighted by their grade, to simplify safety analysis of randomized clinical trials. Lopes et al[6] developed a new metric defined at the individual level by the proportion of the maximum severity of a specific AE over the entire course of the treatment. In the context of clinical trials in which differences in treatment duration or follow-up can be observed, comparisons of tolerance profile through simple AE description may be biased. To address this issue, an AE burden score was computed by Ruppert et al[7] in summing the length of the AE assessment period weighted by the grade of AEs recorded during the period of treatment, divided by the total length of time over which AEs were assessed. As a unifying framework, Le-Rademacher et al[8] included both the frequency and the severity of multiple AEs over time to define an AE burden score. All these scores have been shown to better reflect the global AE burden. They have the potential to become standardized tools to summarize and identify differences of safety profiles between treatments.

Beyond the aim to exhaustively describe safety profiles between treatments, AE scores may be a reliable tool to evaluate toxicity's impact on QoL. In particular, 2 studies by Schuurhuizen and colleagues[9,10] have shown in patients with metastatic disease receiving chemotherapy that cumulative toxicity scores comprising all grades of AEs more accurately predict physical QoL than those limited to high-grade AEs. This finding emphasizes the importance of reporting low-grade AEs in clinical studies. However, their proposed scores did not incorporate longitudinal aspects of AEs, such as duration or time to onset.

This study explored a novel toxicity scoring approach that considers cumulation, grade, and duration of reported AEs to best evaluate toxicity and its impact on QoL. Particular attention has been paid to evaluating the integration of moderate-grade AEs and/or AE duration into the toxicity score and to assess the impact of AEs on QoL according to the nature of AEs (laboratory investigations or nonlaboratory/symptomatic), and their relationship to treatment. This exploratory study was conducted using the AURELIA clinical trial dataset, a randomized open-label phase III trial designed to assess the efficacy of bevacizumab in addition to palliative chemotherapy for patients with PROC.[11]

Methods

Data Source

In the AURELIA study, 361 patients were randomly assigned to receive chemotherapy either alone (CH arm: n=182) or with bevacizumab (BEV + CH arm: n=179).[11] Chemotherapy included paclitaxel, pegylated liposomal doxorubicin (PLD), or topotecan. Adding bevacizumab to chemotherapy significantly improved PFS, with a median PFS of 6.7 months (95% CI, 5.7–7.9 months) in the BEV + CH arm versus 3.4 months (95% CI, 2.2–3.7 months) in the CH arm (log-rank $P<.001$). The objective response rate was in favor of the BEV + CH arm (30.9% vs 12.6%; $P<.001$).

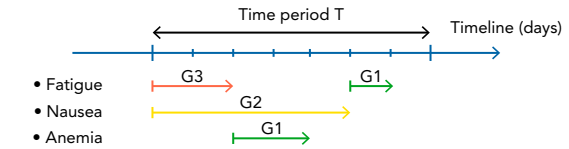
The EORTC QoL Questionnaire-Core 30 (QLQ-C30) is designed to measure the physical, psychological, and social functions of patients with cancer through 30 items scored on a Likert scale,[12] incorporating 5 functional dimensions (physical, role, cognitive, emotional, and social), 3 symptom scales (fatigue, pain, and nausea/vomiting), 6 single items (appetite loss, constipation, diarrhea, dyspnea, insomnia, and financial difficulties), and a global health status. Questionnaires were collected at baseline and every 2 cycles (or 3 cycles for patients receiving every-3-weeks regimens [eg, cycles of treatment lasting 3 weeks]) until the cycle in which progression was determined. Analysis time points were predefined at weeks 8/9, 16/18, 24, and 30.

AEs were collected at each visit, with start and end dates, and graded according to the NCI CTCAE version 3.0 (limited to grade 2 or higher). The imputability of AEs was defined by investigators as possibly or probably related to treatment.

Toxicity Score Definition

Four toxicity scores were calculated per individual patient: the total number of AEs (cumulative score), the total number of AEs multiplied by their grade (severity score), the sum of the number of days spent with each AE (duration score), and the sum of the number of days spent with each AE weighted by its grade (weighted duration score) (Figure 1).

Toxicity scores were computed for the week 8/9 and 16/18 periods. AEs occurring during the first 8/9 weeks were considered for the score of the week 8/9 period. AEs observed between weeks 8/9 and 16/18 were considered for the score of the week 16/18 period. Duration was measured as the time between the start and end dates of the AEs. For AEs still ongoing at weeks 8/9 or 16/18, the end date of AEs was considered as the end date of the week 8/9 or 16/18 period, respectively. When the same AE was



Toxicity scores computed for time period T:
- Cumulative score = 3 *(fatigue + nausea + anemia)*
- Severity score = 6 *(G3 fatigue + G2 nausea + G1 anemia)*
- Duration score = 10 *(3 days fatigue + 5 days nausea + 2 days anemia)*
- Weighted duration score = 20 *([G2*3 days + G1*1 day fatigue] + G2*5 days nausea + G1*2 days anemia)*

Figure 1. Toxicity score calculation for a patient at a fixed time period using fictional data.
Abbreviation: G, grade.

observed multiple times during the same period, it was considered as a unique AE with a maximal grade in both cumulative and severity scores, and the duration was the sum of days experienced with the AE.

Scores were computed considering either all grades of AEs (grade 2–4) or only high-grade AEs (grade 3 or 4) to evaluate the added value of considering grade 2 AEs when assessing the predictive value of toxicity for QoL alteration. Sets of the complete list of AEs or of only nonlaboratory AEs were analyzed separately. We also specifically analyzed AEs related to treatments. The sets of disease-specific AEs were considered for supplementary analyses.[4] Analyses focused on the EORTC QLQ-C30 global health status QoL, which is an overall rating of the health and QoL of patients, and the physical functioning scale, which specifically assesses the capacity for a patient to perform activities of daily living, reflecting treatment toxicities and tumor-related symptoms, and has been shown to be a prognostic value of overall survival in the AURELIA trial.[13]

Statistical Analysis

Linear mixed models were used to describe QoL change over 2 time points during treatment (weeks 8/9 and 16/18) according to toxicity scores (as a time-dependent variable). Models included a random intercept for each patient to account for interindividual variability, and were adjusted for baseline QoL, age, and chemotherapy treatment (paclitaxel, PDL, topotecan), with allocation arm (CH or BEV + CH) by time (weeks 8/9 or 16/18) interaction (with the hypothesis that QoL change may vary according to treatment arm). Standardized coefficients (β) were estimated after converting toxicity scores into Z-scores, allowing direct comparison of the regression coefficients between models and clinical interpretation as well. A restrictive α risk level of 1% was retained to consider the multiplicity of tests.

Results

AE Description

The safety population included 360 patients (1 patient did not receive any study drug and was excluded from analyses). A total of 2,086 AEs were available for analysis, with a median duration of 19 days (minimum 0 days, maximum 739 days), including 1,431 (68.6%) nonlaboratory events (Table 1). Of these, 1,386 (66.4%) were considered to be related to at least one of the study treatments. The number of AEs was higher in the BEV + CH arm (54% vs 46%).

Respectively, 171 (47.5%) and 43 (11.9%) patients experienced at least one grade 3 or 4 AE, respectively,

Table 1. AE Description of AURELIA Trial Dataset Used for Analyses

	Total Sample n (%)	BEV + CH Arm n (%)	CH Arm n (%)
Number of events			
All AEs	2,086 (100)	1,126 (100)	960 (100)
Grade 2	1,557 (74.6)	863 (76.6)	694 (72.3)
Grade 3	474 (22.7)	233 (20.7)	241 (25.1)
Grade 4	55 (2.7)	30 (2.7)	25 (2.6)
Nonlaboratory	1,431 (68.6)	752 (66.8)	679 (70.7)
Grade 2	1,094 (76.4)	591 (78.6)	503 (74.1)
Grade 3	303 (21.2)	145 (19.3)	158 (23.3)
Grade 4	34 (2.4)	16 (2.1)	18 (2.6)
Treatment-related	1,386 (66.4)	842 (74.8)	544 (56.7)
Grade 2	1,037 (74.8)	642 (76.2)	395 (72.6)
Grade 3	311 (22.4)	175 (20.8)	136 (25)
Grade 4	38 (2.7)	25 (3.0)	13 (2.4)
Number of patients			
Maximal grade	360 (100)	179 (100)	181 (100)
Grade 2	113 (31.4)	56 (31.3)	57 (31.5)
Grade 3	171 (47.5)	82 (45.8)	89 (49.2)
Grade 4	43 (11.9)	25 (14.0)	18 (9.9)
Treatment-related	285 (79.2)	153 (85.5)	132 (72.9)
Grade 2	120 (33.3)	63 (35.2)	57 (31.5)
Grade 3	134 (37.2)	70 (39.1)	64 (35.4)
Grade 4	31 (8.6)	20 (11.2)	11 (6.1)

Abbreviations: AE, adverse event; BEV, bevacizumab arm; CH, chemotherapy arm.

whereas 113 (31.4%) experienced maximal-grade 2 AEs and 33 (9.2%) did not experience any grade ≥2 AEs. The most frequently observed AEs were fatigue (30.3%), neutropenia (28.6%), anemia (23.9%), abdominal pain (20%), and hypertension (15.3%) (supplemental eTable 1, available with this article at JNCCN.org).

Toxicity Scores

Toxicity scores were available for 360 patients during the week 8/9 period and for 346 patients during the week 16/18 period (supplemental eTable 2). Considering only grade 3/4 AEs, 222 (61.7%) patients were free of AEs (null score) during the week 8/9 period and 228 (65.9%) were free of AEs during the week 16/18 period. Considering all AEs, the number of patients free of AEs was 83 (23.1%) and 96 (27.7%) during the 2 time periods, respectively.

Relation Between Toxicity Scores and QoL

The standardized β of the multivariable association between QoL and toxicity scores computed with laboratory and nonlaboratory AEs is depicted in Figure 2. The global QoL score was not significantly associated with any of the 4 scores, regardless of AE grade and relationship to treatment. The physical QoL score was significantly associated with each of the scores when considering all grades of AEs (all $P<.01$) and with only cumulative and severity scores when only grade 3/4 AEs were included in the scoring procedure.

When global QoL was restricted to treatment-related AEs, it was not associated with any of the 4 toxicity scores, whatever the AE grade (all $P>.01$). The physical QoL score was associated with all 4 toxicity scores when considering all grades of treatment-related AEs (all $P<.01$) and with none of them when considering grade 3/4 AEs only (all $P>.01$). The strength of the association was of the same order regardless of whether the duration was included in the scoring procedure (β varying from –2.27 to –2.52). The strength of the association was stronger with physical QoL when all AEs were considered than when only treatment-related AEs were considered, with β varying from –2.07 to –4.05 versus –0.84 to –2.52, respectively.

The standardized β of the multivariable association between QoL and toxicity scores computed with nonlaboratory AEs is depicted in Figure 3. Global QoL

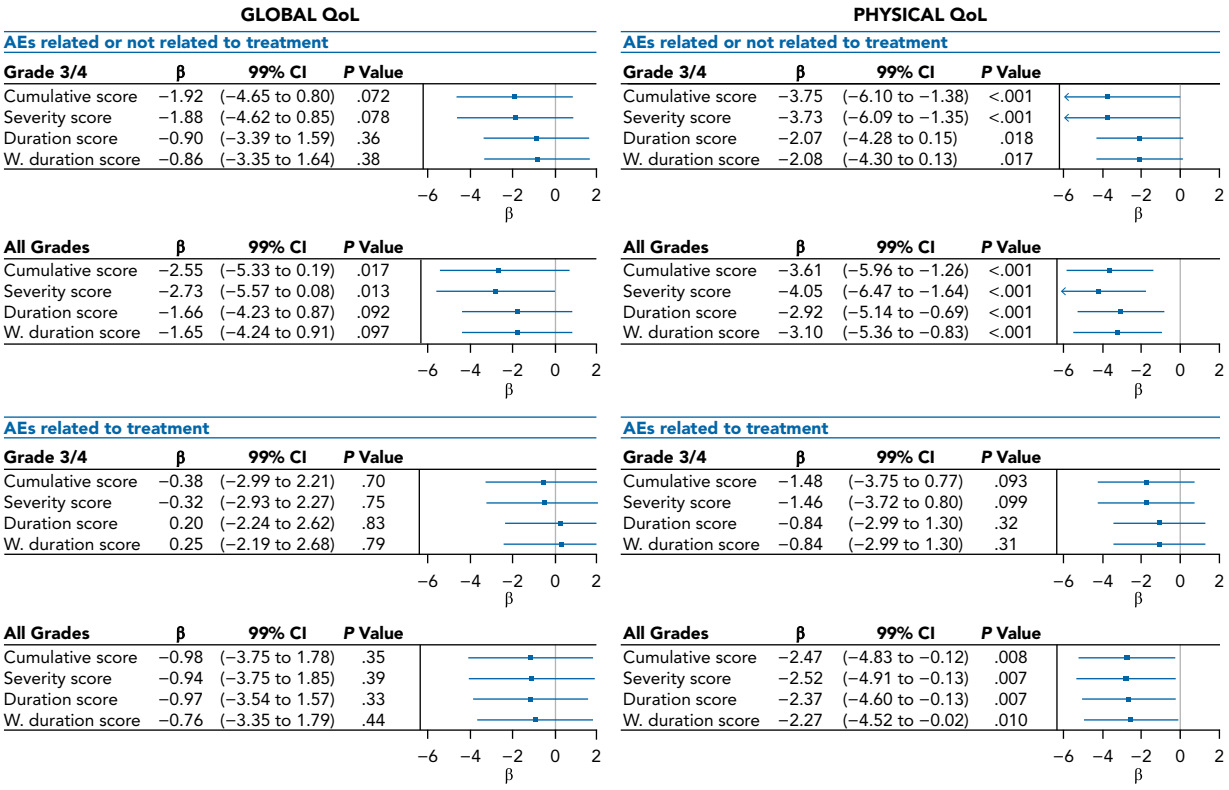


Figure 2. Association between toxicity scores computed with laboratory and nonlaboratory AEs and QoL.
Standardized β estimates and 99% CIs are from a logistic mixed model on QoL score (global or physical) with discrete time (weeks 8/9 or 16/18) and a random patient effect, which includes as independent fixed factors baseline QoL, age, and chemotherapy treatment (paclitaxel, PLD, or topotecan), with allocation arm (CH or BEV + CH) by time interaction. The β value of X indicates that a change of 1 standard deviation in the toxicity score results in an X standard deviation increase in the QoL score (showing QoL improvement when β is positive and deterioration when β is negative). Higher scores of QoL indicate better QoL.
Abbreviations: AE, adverse event; BEV, bevacizumab arm; CH, chemotherapy arm; PLD, pegylated liposomal doxorubicin; QoL, quality of life; W, weighted.

was associated with cumulative and severity scores when we considered all grades of nonlaboratory AEs (with β = –3.13, *P*=.003, and β = –3.42, *P*=.002, respectively) but with none of the 4 scores when considering only grade 3/4 AEs. The physical QoL score was significantly associated with each of the computed scores when considering all grades of AEs (all *P*<.01), with a stronger association when including only grade 3/4 AEs. Moreover, the strength of the association between physical QoL and the cumulative or severity score computed with grade 3/4 AEs was higher than that between physical QoL and the duration or weighted duration score (β = –5.22 or β = –5.29 vs β = –3.02 or –3.09, respectively).

Global QoL was not associated with any of the 4 toxicity scores when we considered treatment-related AEs, including all grades or only grade 3/4 AEs (all *P*>.01). The physical QoL score was associated with the severity and weighted duration score when we considered all treatment-related AEs (β = –2.62; *P*=.006, and β = –2.42; *P*=.008, respectively), and with the cumulative and severity scores when considering only grade 3/4 treatment-related AEs (β = –2.52; *P*=.007, and β = –2.55; *P*=.007, respectively).

Neither global nor physical QoL was associated with any of the 4 toxicity scores computed with laboratory AEs, regardless of whether they were treatment-related or not (data not shown). Global and physical QoL were associated with all severity and cumulative toxicity scores computed with all grades of disease-specific AEs, but not with grade 3/4 AEs (supplemental eFigure 1). Physical QoL was associated with duration scores computed with all grades of disease-specific AEs.

Discussion

This study aimed to evaluate the association between different modes of toxicity reporting and QoL in patients with PROC. The individual safety profile of patients was summarized into scores that included the nature, grade, time of onset, duration, and causality of AEs. Using the AURELIA trial dataset seemed to be specifically appropriate in this context because it comprised a population with an important symptomatic tumor burden in which treatments induce multiple toxicities.[1]

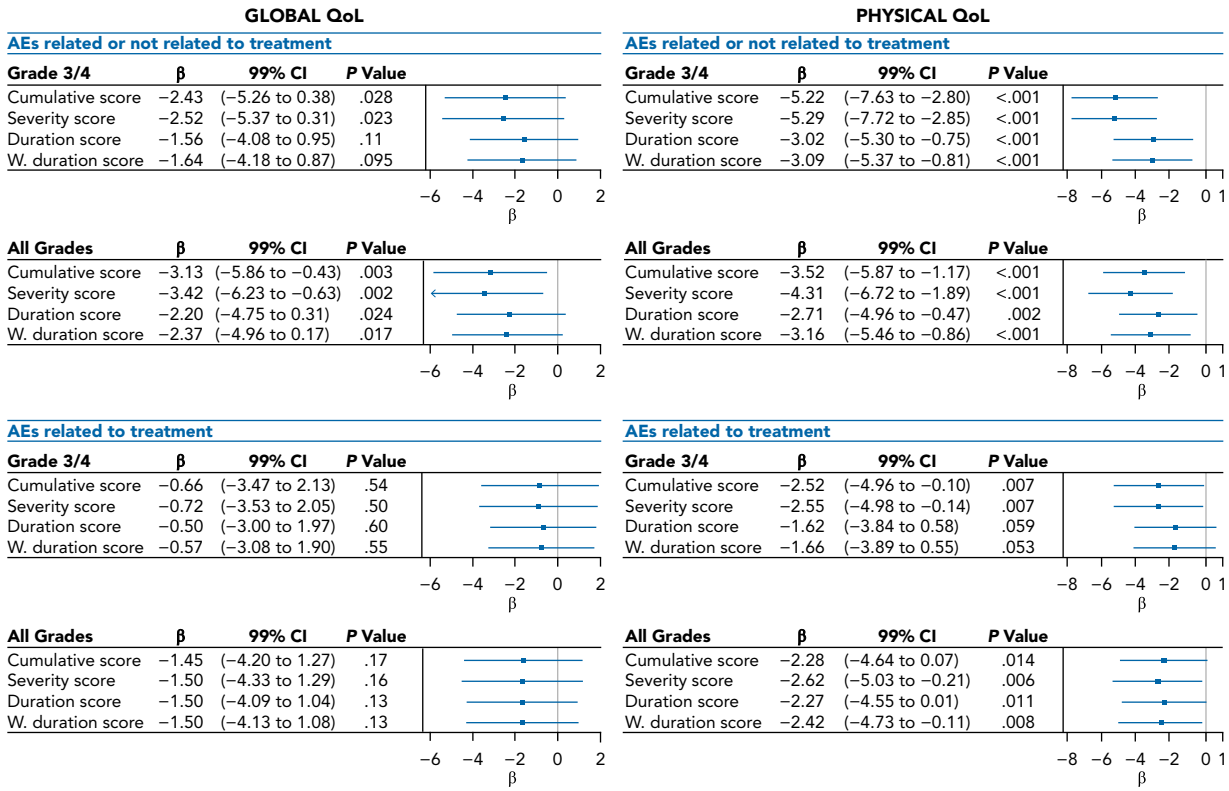


Figure 3. Association between toxicity scores computed with nonlaboratory AEs and QoL.
Standardized β estimates and 99% CIs are from a logistic mixed model on QoL score (global or physical) with discrete time (weeks 8/9 or 16/18) and a random patient effect, which includes as independent fixed factors baseline QoL, age, and chemotherapy treatment (paclitaxel, PLD, or topotecan), with allocation arm (CH or BEV + CH) by time interaction. The β value of X indicates that a change of 1 standard deviation in the toxicity score results in an X standard deviation increase in the QoL score (showing QoL improvement when β is positive and deterioration when β is negative). Higher scores of QoL indicate better QoL.
Abbreviations: AE, adverse event; BEV, bevacizumab arm; CH, chemotherapy arm; PLD, pegylated liposomal doxorubicin; QoL, quality of life; W, weighted.

Our study shows a significant association between physical QoL and the various toxicity scores. However, the relationship between toxicity and physical QoL was strongest when AEs were taken into account regardless of their relationship to treatment, and when laboratory investigation AEs were excluded. An association between global QoL and toxicity was observed only when grade 2 AEs were included in addition to grade 3/4 AEs within the scores of nonlaboratory AEs, independent of their imputability. In addition, both scores, based on the sum of toxicities experienced by each patient, modulated (severity score) or not (cumulative score) by their maximum grade, outperformed the scores based on AE duration.

Different authors have constructed toxicity scores to describe and summarize toxicity profiles in clinical trials.[5–8] However, only Schuurhuizen and colleagues[9,10] explored the impact of cumulative toxicity on QoL through toxicity scores, including the number and grades of nonlaboratory AEs, using 2 different clinical trial datasets of patients with metastatic colorectal and prostate cancer. Results showed that the physical QoL was more affected by cumulative toxicity than the global QoL, and that the association of toxicity scores with physical QoL was stronger when including all grades of AEs versus only severe-grade AEs in the scoring, which is consistent with our results. Similar results were previously found in chronic myelogenous leukemia, in which low-grade AEs have been shown to significantly impair QoL.[14] Therefore, in a palliative setting, clinicians should improve reporting of low-grade AEs in pivotal phase III trials to enhance knowledge about the drug toxicity profile on patients' QoL.[14–16] However, the reporting of low-grade AEs may be challenging, especially when assessed by clinicians. Previous works have examined the relationship between toxicities reported by patients and toxicities reported by physicians,[3,15,16] and have observed an underreporting of symptoms in terms of frequency, severity, and onset, specifically for observable symptoms (vomiting), in contrast with more self-reported symptoms (eg, pain, dyspnea). Authors have explained that patients use an intraindividual comparison to answer questionnaires, whereas physicians use an interindividual comparison based on their clinical experience. Moreover, physicians usually focus on toxicities, which require supportive care intervention, whereas patients worry about all symptoms that impact QoL, which could be less severe and more various.

The originality of this study was to include duration in the scoring procedure to measure the association with QoL. Lopes et al[6] introduced a longitudinal assessment of toxicity by constructing AE summary metrics, including the weighted duration score, to compare the toxicity burden of different chemotherapies in patients with metastatic colorectal cancer. The authors showed that their proposed metric provided relevant additional information compared with traditional AE reports. In this study, we failed to show the added value of considering the duration of toxicities in the scoring procedure when searching for an association with QoL. However, we emphasize that the occurrence of cumulative AEs during a prespecified period is predictive of altered, subsequently assessed QoL.

In our study, we proposed to perform separated analyses by considering all AEs on the one hand, and laboratory or nonlaboratory AEs on the other. Indeed, Greimel et al[3] showed an absence of correlation between patient experience reported by the EORTC QLQ-C30 and hematologic toxicities in patients with ovarian cancer. Similarly, Kristensen et al[17] observed that hematologic toxicity was not associated with global or physical EORTC QLQ-C30 scales in non–small cell lung cancer. As a supplementary analysis, we considered AEs specific to PROC. Indeed, Butler et al[4] found that a restricted number of AEs could explain variation in global QoL in these patients, especially gastrointestinal disorders, urinary frequency, motor weakness, and fatigue. Similarly, we found that global QoL was associated with disease-specific toxicity scores computed with moderate- and severe-grade AEs. However, toxicity scores considered multiple AEs simultaneously, whereas Butler et al[4] considered AEs separately, and the lack of severe or moderate symptoms in their database makes it difficult to offer any conclusive statements. Schuurhuizen and colleagues[9,10] focused on nonlaboratory AEs to compute toxicity scores, which remains to consider only symptomatic AEs. Furthermore, we chose to compute toxicity scores considering both all AEs and only nonlaboratory AEs; our results show a stronger association with QoL when considering only the latter.

In this study, the association between toxicity scores and physical QoL was stronger when all AEs rather than only treatment-related AEs were included. PROC is a symptomatic disease that is known to impact baseline QoL of patients. Lee et al[1] reported reduced baseline QoL in 87% of patients and that chemotherapy allowed an improvement of QoL in 20% of patients within a median time of 5 weeks. Therefore, all AEs must be taken into account when assessing toxicity in patients with PROC.

This study has several limitations. Evaluation of the impact of AE duration on QoL could have been limited by the short duration of the treatment (maximum of 18 weeks), because of the unfavorable prognosis of the disease. Scores based on AE duration need to be reassessed in the context of current maintenance treatments, which may last years. In addition, measurement of the impact of lower-grade AEs on QoL was not performed because of the absence of grade 1 AE collection in the AURELIA trial. Finally, no PRO-CTCAE data were collected in this study. Because PRO-CTCAE

items are known to be only weakly correlated with clinician-reported AEs,[3] the analysis of such data would be of great interest.[15,16,18]

Conclusions

Toxicity scores allow the reporting of toxicity and are shown to be associated with patients' QoL. Our analysis contributes to identifying AEs to consider within these scores, highlighting the importance of considering moderate-grade and symptomatic AEs in clinical trials due to their significant impact on QoL. The cumulative aspect of AEs is included in the scoring procedure by summing over the number of AEs observed during a prespecified period, which is rarely explored in safety analyses. Taking into account AEs, regardless of whether they are treatment-related, better reflects the association between toxicity and QoL. To deliver exhaustive information for making the best choice of treatment in a palliative situation, AEs should be thoroughly reported in phase III trials, with specifications for their relationship to treatment and particular attention to low-/moderate-grade AEs.[15,19]

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Supplemental online content for:

Evaluation of Scores to Reflect Toxicity Impact on Quality of Life of Patients With Platinum-Resistant Ovarian Cancer: AURELIA Substudy

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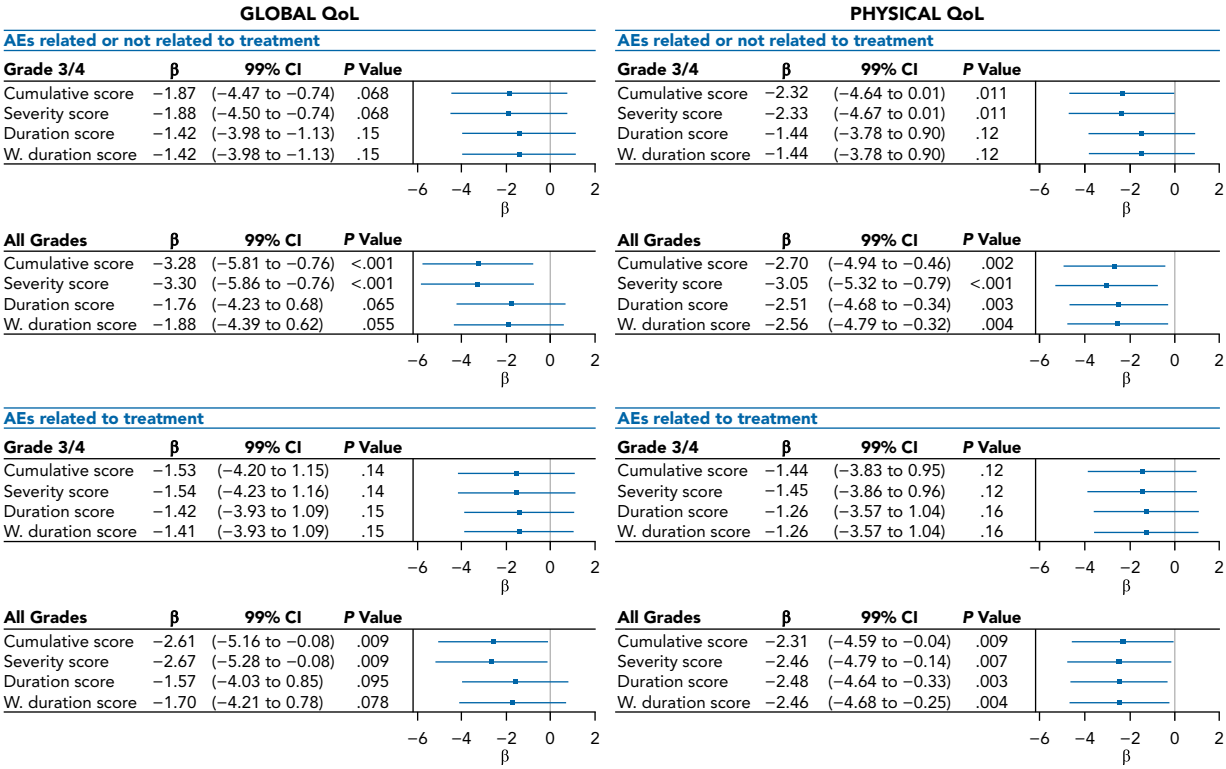

eFigure 1. Association between toxicity scores computed with disease-specific AEs and QoL.
Disease-specific AEs has been defined as AEs observed in at least 10% of patients (fatigue, abdominal pain, hypertension, peripheral neuropathy, and vomiting; see supplemental eTable 1) plus AEs shown to be associated with QoL change (constipation, myalgia, and insomnia).[1] Standardized β estimates and 99% confidence intervals are from a logistic mixed model on QoL score (global or physical) with discrete time (week 8/9 or 16/18) and a random patient effect, which includes as independent fixed factor baseline QoL, age, and chemotherapy treatment (paclitaxel, PLD, or topotecan), with allocation arm (CT or BEV + CT) by time interaction. β value of X indicates that a change of one standard deviation in the toxicity score results in an X standard deviation increase in the QoL score (showing QoL improvement when β is positive, and deterioration when β is negative). Higher scores of QoL indicate better QoL.
Abbreviations: AE, adverse event; BEV, bevacizumab arm; CH, chemotherapy arm; PLD, pegylated liposomal doxorubicin; QoL, quality of life; W, weighted.

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eTable 1. Most Frequently Observed AEs (>2% of Total Sample)

AEs (PTNAME, MedDRA Classification)	All Grades n (%)	Grade 2 n (%)	Grade 3/4 n (%)
Fatigue	109 (30.3)	78 (21.7)	31 (8.6)
Abdominal pain	72 (20)	50 (13.9)	22 (6.1)
Hypertension	55 (15.3)	36 (10)	19 (5.3)
Peripheral neuropathy	50 (13.9)	37 (10.3)	13 (3.6)
Vomiting	38 (10.6)	27 (7.5)	11 (3.1)
Constipation	35 (9.7)	32 (8.9)	3 (0.8)
Infections – pathogen unspecified	35 (9.7)	35 (9.7)	0 (0)
Nausea	34 (9.4)	31 (8.6)	3 (0.8)
Mucosal inflammation	34 (9.4)	30 (8.3)	4 (1.1)
Skin disorders	33 (9.2)	28 (7.8)	5 (1.4)
Urinary tract infection	32 (8.9)	31 (8.6)	1 (0.3)
Nail disorders	32 (8.9)	19 (5.3)	13 (3.6)
Diarrhea	31 (8.6)	19 (5.3)	12 (3.3)
Hand–foot reaction	30 (8.3)	19 (5.3)	11 (3.1)
Dyspnea	27 (7.5)	17 (4.7)	10 (2.8)
Alopecia	27 (7.5)	27 (7.5)	0 (0)
Infection without neutropenia	26 (7.2)	22 (6.1)	4 (1.1)
Decreased appetite	25 (6.9)	20 (5.6)	5 (1.4)
Bleeding	23 (6.4)	18 (5)	5 (1.4)
Pain	25 (6.9)	22 (6.1)	3 (0.8)
Weight increased/decreased	20 (5.6)	18 (5)	2 (0.6)
Pyrexia	20 (5.6)	20 (5.6)	0 (0)
Thromboembolic events: venous	18 (5)	5 (1.4)	13 (3.6)
Subileus	17 (4.7)	6 (1.7)	9 (2.5)
Arthralgia/Myalgia	13 (3.6)	13 (3.6)	0 (0)
Ascites	12 (3.3)	6 (1.7)	6 (1.7)
Gastroenteritis	12 (3.3)	11 (3.1)	1 (0.3)
Bone disorder	12 (3.3)	9 (2.5)	3 (0.8)
Fistula/Abscess	12 (3.3)	8 (2.3)	4 (1.1)
Allergic reaction	11 (3.1)	10 (2.8)	1 (0.3)
Headaches	11 (3.1)	11 (3.1)	0 (0)
Cystitis	11 (3.1)	10 (2.8)	1 (0.3)
Pleural effusion	8 (2.2)	3 (0.8)	5 (1.4)
Laboratory AEs			
Neutropenia	103 (28.6)	43 (11.9)	60 (16.7)
Anemia	86 (23.9)	77 (21.4)	9 (2.5)
Leucopenia	48 (13.3)	28 (7.8)	20 (5.6)
Thrombocytopenia	28 (7.8)	20 (5.6)	8 (2.2)
Proteinuria	26 (7.2)	21 (5.8)	5 (1.4)
GGT/ASAT/ALAT	14 (3.9)	6 (1.7)	8 (2.3)
Lymphopenia	11 (3.1)	7 (2.0)	4 (1.1)

Abbreviations: AE, adverse event; ALAT, alanine aminotransferase; ASAT, aspartate aminotransferase; GGT, gamma-glutamyl transferase; PTNAME, Preferred Term Name.

eTable 2. Descriptive Statistics of Toxicity Scores

	Both Periods	Week 8/9	Week 16/18
All AEs, N	**706**	**360**	**346**
Grade 3/4			
Null score,[a] n (%)	450 (63.7%)	222 (61.7%)	228 (65.9%)
Mean [SD]			
Cumulative score	0.6 [1.0]	0.66 [1.1]	0.54 [0.9]
Severity score	1.86 [3.13]	2.03 [3.4]	1.68 [2.8]
Duration score	13.22 [26.0]	13.12 [23.7]	13.3 [28.2]
Weighted duration score	40.54 [79.0]	40.4 [72.6]	40.7 [85.3]
All grades			
Null score,[a] n (%)	179 (25.4%)	83 (23.1%)	96 (27.7%)
Mean [SD]			
Cumulative score	2.19 [2.1]	2.27 [2.2]	2.12 [2.0]
Severity score	4.99 [4.9]	5.18 [5.1]	4.79 [4.6]
Duration score	48.04 [57.1]	43.18 [50.2]	53.08 [63.2]
Weighted duration score	110.2 [130.8]	100.53 [117.4]	120.2 [142.9]
Nonbiological AEs, N	**706**	**360**	**346**
Grade 3/4			
Null score,[a] n (%)	525 (74.4%)	268 (74.4%)	257 (74.3%)
Mean [SD]			
Cumulative score	0.40 [0.8]	0.4 [0.8]	0.40 [0.8]
Severity score	1.23 [2.5]	1.24 [2.6]	1.23 [2.5]
Duration score	8.62 [21.5]	7.6 [18.0]	9.80 [24.6]
Weighted duration score	26.44 [65.1]	23.3 [55.2]	29.93 [74.3]
All grades			
Null score,[a] n (%)	239 (33.9%)	118 (32.8%)	121 (35.0%)
Mean [SD]			
Cumulative score	1.60 [1.8]	1.59 [1.8]	1.62 [1.7]
Severity score	3.62 [4.0]	3.58 [4.1]	3.66 [3.9]
Duration score	35.43 [49.6]	29.68 [41.8]	41.42 [56.0]
Weighted duration score	80.07 [112.4]	67.48 [95.9]	93.17 [126.2]

(*continued on next page*)

eTable 2. Descriptive Statistics of Toxicity Scores (cont.)

	Both Periods	Week 8/9	Week 16/18
Disease-Specific AEs, N	**706**	**360**	**346**
Grade 3/4			
Null score,[a] n (%)	643 (91.1%)	324 (90%)	319 (92.2%)
Mean [SD]			
Cumulative score	0.1 [0.3]	0.11 [0.3]	0.08 [0.3]
Severity score	0.29 [0.9]	0.33 [1.0]	0.25 [0.9]
Duration score	2.62 [10.7]	2.66 [9.6]	2.58 [11.7]
Weighted duration score	7.87 [32.1]	7.99 [28.9]	7.73 [35.1]
All grades			
Null score,[a] n (%)	482 (68.3%)	241 (66.9%)	241 (69.7%)
Mean [SD]			
Cumulative score	0.4 [0.7]	0.43 [0.7]	0.37 [0.6]
Severity score	0.89 [1.5]	0.96 [1.5]	0.81 [1.4]
Duration score	8.72 [19.1]	8.23 [17.2]	9.24 [20.9]
Weighted duration score	20.08 [45.1]	19.14 [40.4]	21.05 [49.5]

Abbreviations: AE, adverse event; PTNAME, preferred term name.
[a]No AE was observed during the period.