Optimizing psychosocial support and symptom management for patients with advanced cancer

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2019

document version
Publisher's PDF, also known as Version of record

CHAPTER 8

The predictive value of patient- and clinician-reported cumulative toxicity for quality of life in patients with metastatic castrate-naïve prostate cancer

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Accepted for publication in Journal of the National Comprehensive Cancer Network: In press

Abstract

Background

Current toxicity evaluation is primarily focused on high-grade adverse events (AEs) reported by clinicians. However, the cumulative effect of multiple lower grade AEs may also impact patients' quality of life (QOL). Further, patient-reported toxicity may be more representative for patients' treatment experiences. This study aimed to determine whether cumulative toxicity comprising all grades AEs is more associated with QOL than cumulative toxicity comprising high-grade AEs only, and whether patient-reported cumulative toxicity is more associated with QOL than clinician-reported cumulative toxicity.

Methods

Patients with metastatic castrate-naïve prostate cancer (mCNPC) participating in the phase III GETUG-AFU-15 trial, completed questionnaires on AEs (at 3 and 6 months) and QOL (at baseline, 3 and 6 months). Clinicians reported AEs during clinical visits. Cumulative toxicity scores were calculated for clinicians and patients in three ways: total number of high-grade AEs, total number of all grades AEs, and total number of all AEs multiplied by their grade (severity score). Relations between cumulative toxicity scores and QOL were studied using longitudinal regression analyses; unstandardized (B) and standardized regression coefficients (Beta) are reported.

Results

Out of 385, 184 patients with complete QOL and toxicity data were included. The clinician-reported all grades AEs (B=-2.2,95%CI=-3.3;-1.1,p<0.01) and severity score (B=-1.4,95%CI=-2.2;-0.7,p<0.01) were associated with deteriorated physical QOL, while the total of high-grade AEs was not. All patient-reported scores were significantly (all $p's$ <0.01) related to deteriorated physical and global QOL. Standardized regression coefficients indicated that patient-reported toxicity scores were more associated with QOL outcomes than clinician-reported scores, with the strongest association found for the all-grade and severity cumulative toxicity scores.

Conclusion

Patient and clinician-based cumulative toxicity scores comprising all grades AEs better reflect the impact on patients' QOL than toxicity scores comprising high-grade AEs only. To assess the impact of toxicity on QOL,

patient-reported cumulative toxicity scores are preferred.

Introduction

In daily oncology practice, clinicians constantly weigh the expected benefit of treatment against the exposure to possible treatment-related adverse events (AEs)[1]. Especially in patients with advanced disease, for whom the survival benefit of (systemic) treatments may be limited, the number and extent of AEs and their impact on a patient's quality of life (QOL) are important[2]. Providing a representative overview of treatment-related AEs is essential for patients to make an informed decision to undergo treatment[3,4].

Currently, the main source of information on toxicity in randomized controlled trials (RCTs) is a clinician-based assessment of AEs during clinic visits, following the National Cancer Institute's (NCI) Common Terminology Criteria for Adverse Events (CTCAE)[5,6]. This may be suboptimal, as the reporting of AEs in RCTs is primarily focused on high-grade AEs (grade 3-4) while the lower grade AEs are not always incorporated[7]. Although a description of high-grade toxicities is important and relevant to determine drug safety, patients' QOL is also likely to be influenced by the often daily (re)occurring, longer-lasting grade 1 or 2 AEs throughout therapy, since these determine drug tolerability. We recently studied the burden of cumulative toxicity in patients with colorectal cancer and found that cumulative toxicity scores comprising all grade AEs were associated with patients' physical QOL, while the total score of high-grade AEs was not[8]. The cumulative toxicity scores reported in our study were based on clinician-reported AEs, whereas the accuracy of assessment and reporting of AEs by clinicians has been recently questioned[8]. Symptomatic AEs associated with anticancer treatments seem to be underreported by clinicians, also when data are prospectively collected within RCTs[9,10]. Patient-reported outcomes (PROs) to assess AEs may provide an alternative measure for patients' treatment experiences[11].

The purpose of this prospective study in patients with metastatic castrate-naïve prostate cancer (mCNPC) was to determine whether i) cumulative toxicity comprising all grades AEs (grade 1-4) is more associated with QOL than cumulative toxicity comprising high-grade AEs only (grade 3-4); and ii) cumulative toxicity reported by patients is more associated with QOL than cumulative toxicity reported by clinicians .

Methods

This is a secondary analysis on data obtained in the prospective Genito-Urinary Oncology Group (GETUG)-AFU 15 trial[12]. This multicenter, randomized, open-label phase III trial evaluated the efficacy and safety of docetaxel combined with androgen-deprivation therapy (ADT) compared to ADT alone on overall survival in patients with mCNPC. The study was approved by the 'French Comité de Protection des Personnes' and written consent was obtained for all patients (ClinicalTrials.gov, number NCT00104715). Results of the original trial have been published previously[12]. In brief, there was no significant difference in overall survival between the treatment arms although progression free survival was significantly improved in the docetaxel group.

Patients

In total, 385 patients with mCNPC were enrolled between October 2004 and December 2008 in the GETUG-AFU 15 trial. For the current analyses, we included patients who completed QOL assessments prior to and 3 or 6 months after the start of treatment, and for whom patient- and clinician-reported toxicity data was available.

Study design and measurements

Patients completed QOL questionnaires at baseline (prior to the start of first line treatment) and after 3 and 6 months of treatment. Clinicians reported on AEs during clinical visits, which occurred every 3 weeks in the group treated with ADT plus docetaxel and every 3 months in the group treated with ADT alone. Patient were invited to complete a questionnaire on AEs 3 and 6 months after the start of treatment, immediately before or after toxicity evaluation by their clinicians. This questionnaire was adapted from a previous study[13] and consisted of 26 items describing 22 symptoms often associated with docetaxel and castration treatments. For each symptom patients were asked whether it occurred during the previous month (yes/no) and the extent of subjective disturbance that they experienced (four-point Likert scale from 1=not at all to 4=very much).
We looked for the same 22 symptoms reported by clinicians at the 3- and 6-month clinical visit from patient records and graded these using the National Cancer Institute's Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 3.0.

CTCAE items representing single AEs were graded on a four-point Likert scale (1=mild and 4=life threatening). Grade 3 and 4 AEs generally indicate the need for clinical action[6]. If a symptom was not mentioned it was

considered to be absent. Following the approach from our previous study[8], physical function and global QOL were assessed with subscales of the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-C30 (EORTC QLQ-C30). This cancer-specific QOL questionnaire is internationally validated and widely used[14]. A change in QOL of at least 10 points is regarded as a minimal clinically important difference (MCID)[15,16]. Additionally, patient demographic, tumor and treatment characteristics, and Eastern Cooperative Oncology Group Performance Score (ECOG PS) were extracted from patient records. Progression during the first 3 or 6 months of treatment comprised biochemical progression, clinical progression or death as defined in the original trial[12].

Statistical analysis

Descriptive analyses were performed to summarize patient demographic, tumor, and treatment characteristics and QOL. Multivariate logistic regression analyses were used to compare characteristics of patients from the GETUG-AFU 15 trial that were included in the current analyses with patients that were excluded, and to compare characteristics of patients with missing data with patients without missing data. The prevalence of the specific types of NCI CTCAE grade AEs was calculated. For each patient, we calculated the clinician-based cumulative toxicity scores in three ways: i) high-grade cumulative toxicity score as the total number of severe AEs (grade 3-4), ii) all-grade cumulative toxicity score as the total number of AEs (all grades), and iii) the severity cumulative toxicity score as the sum of the total number of all AEs multiplied by their grade[8].

Each of the 22 symptoms reported as being present by patients was graded from 1-4 analogous to the rating of subjective disturbance. In case symptoms were absent these were being coded 0. Subsequently, patient-reported cumulative toxicity scores were calculated in an identical manner as the clinician-based cumulative toxicity scores. To test the degree of agreement between the mean cumulative toxicity scores reported by patients and clinicians, intraclass correlation coefficients (ICC) were calculated using Two-Way Random-Effects Models[17]. An ICC value less than 0.5 indicates poor agreement, values between 0.5 and 0.75 moderate, between 0.75 and 0.9 good, and greater than 0.9 excellent[17]. Mean changes in physical and global QOL over time were evaluated using longitudinal regression analyses.

Associations between each of the cumulative toxicity scores and physical and global QOL at 3 and 6 months

were evaluated using longitudinal regression analyses (linear mixed models, LMM). The models were adjusted for QOL at baseline[18]. The LMM handles missing data automatically under the Missing At Random assumption. We built separate models for each of the clinician-reported and the patient-reported cumulative toxicity scores. In the multivariate regression models we adjusted for the following covariates: age, ECOG PS, progression during treatment (yes vs no), baseline QOL, allocation to treatment arm in the GETUG-AFU 15 trial, metastatic volume (high vs low, where high metastatic volume is defined as: the presence of visceral metastases and/or at least four bone lesions, including at least one bone structure beyond the spine or pelvis)[19], serum concentration of prostate specific antigen (psa) at start treatment (<65 or ≥65 ng/ml), and Gleason score at baseline (2-6 vs 7 vs 8-10).

Unstandardized (B) and standardized regression coefficients (Beta) and 95% CIs were reported, allowing clinical interpretation (B) and direct comparison (Beta) of the obtained regression coefficients in the different models, respectively. The standardized regression coefficients were determined by conducting the LMM on the QOL and toxicity data after converting these data into Z-scores[20]. For all statistical analyses, a p-value smaller than 0.05 was considered statistically significant. Data were analyzed using IBM SPSS statistics version 22.0 (IBM Corp., Armonk, NY).

Results

Patient characteristics of the GETUG-AFU 15 trial are presented in Table 1. In total, 201 of the 385 patients enrolled were not eligible for current analyses due to completely missing QOL questionnaires and/or toxicity data (Figure 1). Consequently, data from 184 patients were included. There were no significant differences in baseline demographic and clinical characteristics between the 184 patients included and the 201 patients excluded from the analyses (Table 1). Cumulative clinician-reported scores were available for 183 (99.5%) and 120 (65.2%) patients at 3 and 6 months after start of treatment, respectively (Table 2). Additionally, 168 (91.3%) patients completed the patient-reported AEs at 3 months after start of treatment, and 107 (58.2%) patients at 6 months after start of treatment (Table 2). Missing data in one or more QOL or toxicity assessments were present in 100 patients. Patients with missing values were more likely to have been allocated to the intervention (ADT + docetaxel) arm (68% versus 44%) and to have had progressive disease (12% versus 7%) during treatment than patients without missing values (data not shown).

Mean age (SD) of patients included in the current study was 63.5 (7.8) years and 95.1% of patients had an ECOG performance score of 0 before the start of treatment. Mean global QOL changed significantly over time from 66.9 (21.3) at baseline to 68.0 (19.3) at 3 months and 64.4 (19.4) at 6 months after start of treatment (p=0.041). Mean physical QOL reduced significantly over time from 87.2 (16.6) at baseline to 83.4 (18.0) at 3 and 79.3 (18.8) at 6 months ($p \leq 0.001$).

Table 1 Clinical characteristics of the study population

	Population GETUG-15 (n = 385)	Population excluded from cumulative AE study (n = 201)	Population included in cumulative AE study (n = 184)	p-value
Age – yr				0.183
Mean (SD)	63 (7.8)	62.6 (7.8	63.5 (7.8)	
Range	43 – 84	43 - 81	48 - 84	
Serum concentration of prostate-specific antigen (ng/mL)				0.924
Mean (SD)	197.3 (808.6)	271.7 (1084.6)	116.9 (281.7)	
Range	0 - 11900	0 - 11900	0 - 2780	
Missing	4	3	1	
Metastatic extent, n (%)				0.744
Low-volume disease	202 (52.5%)	105 (52.2%)	97 (52.7%)	
High-volume disease	183 (47.2%)	96 (47.8%)	87 (47.3%)	
Treatment arm, n (%)				0.077
ADT + Docetaxel	191 (49.6%)	86 (42.8%)	105 (57.1%)	
ADT	194 (50.4%)	115 (57.2%)	79 (42.9%)	
Initial Gleason score, n (%)				0.124
2-6	32 (8.3%)	13 (6.5%)	19 (10.3%)	
7	130 (33.8%)	63 (31.3%)	67 (36.4%)	
8-10	216 (56.1%)	122 (60.7%)	94 (51.1%)	
Missing	7 (1.8%)	3 (1.5%)	4 (2.2%)	
ECOG performance score, n (%)				0.493
0	357 (97.7%)	182 (90.5%)	175 (95.1%)	
1	9 (2.3%)	6 (3.0%)	3 (1.6%)	
Missing	19 (4.9%)	13 (6.5%)	6 (3.3%)	
EORTC QLQ-C30 Global QOL score				0.648
Mean (SD)	66.6 (21.1)	66.2 (20.7)	66.9 (21.3)	
Range	0 - 100	0 - 100	0 - 100	
Missing	86	86	0	
EORTC QLQ-C30 Physical functioning score				0.450
Mean (SD)	87.8 (16.8)	88.7 (21.3)	87.2 (16.6)	
Range	20 - 100	20 - 100	20 - 100	
Missing	78	78	0	

Reporting of AEs and cumulative toxicity scores

Clinicians reported AEs for 159 (86.9%) and 108 (90%) patients after 3 and 6 months, respectively. At least one high-grade AE (grade 3-4) was reported in 19 (10.4%) patients after 3 months of treatment, and in 24 (20%) patients after 6 months (Table 2). All patients reported to have experienced AEs at 3 and 6 months after start of treatment. In total, 149 (88.7%) patients reported at least one high-grade AE (grade 3-4) after 3 months of treatment, and 93 (86.9%) patients reported them after 6 months of treatment (Table 2). As reported

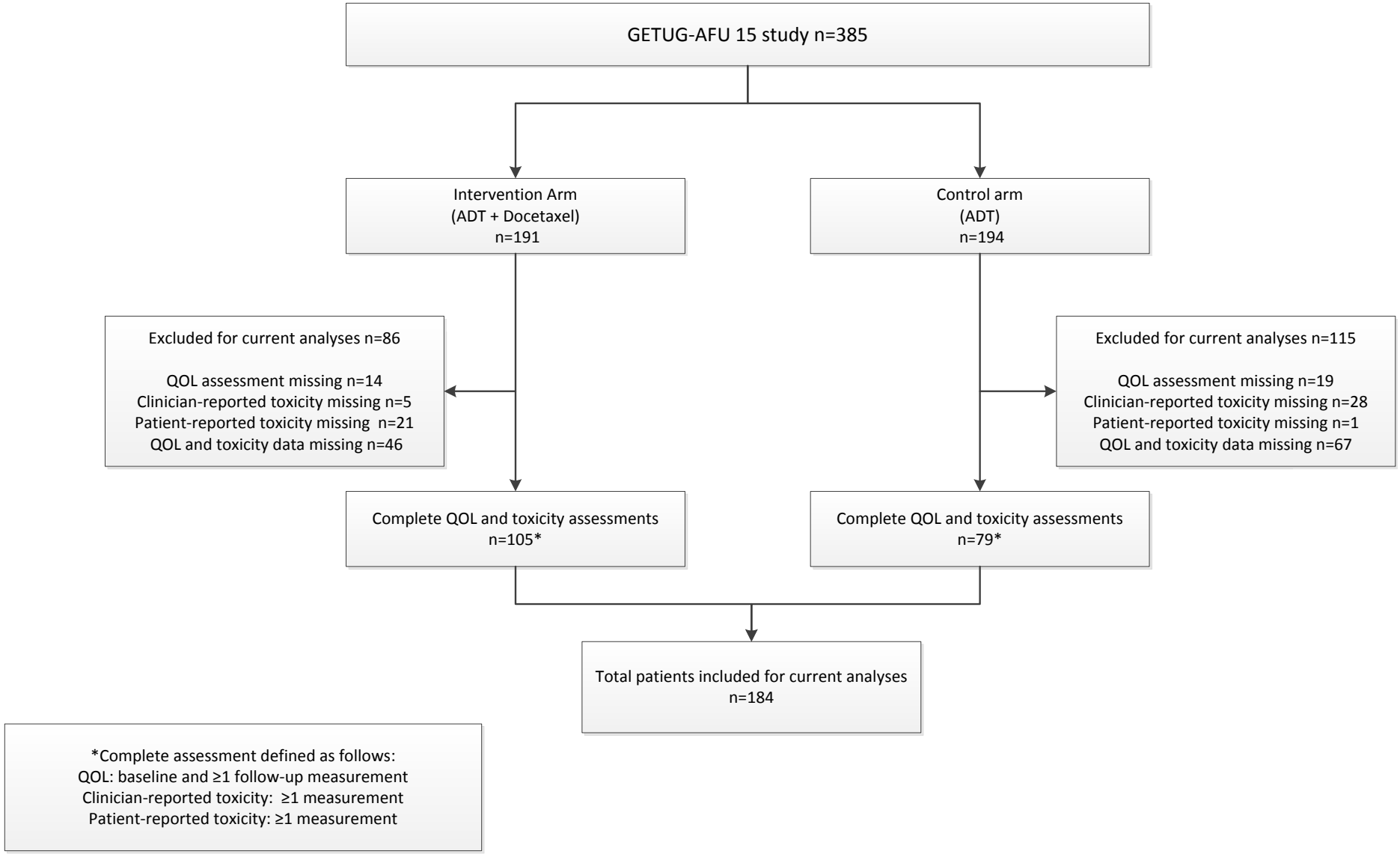

Figure 1 Study flow chart

Table 2 Reporting of adverse events by clinicians and patients						
	Reporting of AEs between baseline – 3 months			Reporting of AEs between 3-6 months		
	Total of patients assessed for toxicity	Any grade AEs, n (%)	High grade AEs, n (%)	Total of patients assessed for toxicity	Any grade AEs, n (%)	High grade AEs, n (%)
Clinicians	183	159 (86.9)	19 (10.4)	120	108 (90)	24 (20)
Patients	168	168 (100)	149 (88.7)	107	107 (100)	93 (86.9)

Abbreviations: AEs= adverse events

Table 3 Mean cumulative toxicity scores and agreement between clinician-reported and patient-reported scores			
	Clinician–reported cumulative toxicity scores Mean (SD)	Patient-reported cumulative toxicity scores Mean (SD)	ICC (95% CI), p-value
High-grade score	0.2 (0.4)	3.1 (2.6)	0.019 (-0.103;- 0.140) *p*=0.382
All-grade score	2.2 (1.9)	7.1 (3.5)	0.344 (0.232;-0.447) *p*=0.000
Severity score	3.1 (2.9)	16.4 (10.2)	0.175 (0.054;-0.290) *p*=0.002

Abbreviations: SD= standard deviation; ICC= intraclass correlation coefficient

Table 4 Cumulative toxicity scores and quality of life outcomes						
	Clinician-reported cumulative toxicity scores			Patient-reported cumulative toxicity scores		
Global QOL	B [95% Confidence Interval for B]	Beta [95% Confidence Interval for Beta]	*p*-value	B [95% Confidence Interval for B]	Beta [95% Confidence Interval for Beta]	*p*-value
High-grade score[b]	2.615 [-2.772;8.001]	0.048 [-0.051;0.147]	.340	-2.813 [-3.654;-1.973]	-0.334 [-0.433;-0.234]	<.001*
All-grade score[c]	-1.215 [-2.525;0.095]	-0.101 [-0.209;0.008]	.069	-2.612 [-3.310;-1.913]	-0.433 [-0.547;-0.317]	<.001*
Severity score[d]	-0.722 [-1.589;0.145]	-0.087 [-0.191;0.017]	.102	-0.909 [-1.136;-0.682]	-0.419 [-0.523;-0.314]	<.001*
Physical QOL						
High-grade score[b]	-3.710 [-8.299;0.879]	-0.877 [-0.196;0.021]	.113	-2.392 [-3.127;-1.657]	-0.364 [-0.476;-0.252]	<.001*
All-grade score[c]	-2.216 [-3.319;-1.113]	-0.236 [-0.353;-0.118]	<.001*	-2.117 [-2.711;-1.523]	-0.450 [-0.577;-0.324]	<.001*
Severity score[d]	-1.446 [-2.181;-0.711]	-0.224 [-0.337;-0.110]	<.001*	-0.806 [-1.002;-0.610]	-0.476 [-0.592;-0.361]	<.001*

[a]Adjusted for the following covariates: age, ECOG PS, progression during treatment (yes vs no), baseline QOL, allocation to treatment arm in the parent study number, metastatic volume (high- or low; the presence of visceral metastases and/or at least four bone lesions, including at least one bone structure beyond the spine or pelvis)[15], serum concentration of prostate specific antigen (psa) at start treatment (<65 or ≥65 ng/ml), and Gleason score at baseline (2-6, 7, 8-10).

[b]Total number of severe AEs (grade 3-4). [c]Total number of AEs (all grades). [d]Sum of total number of all grades AEs multiplied by their grade. Abbreviations:

B = unstandardized regression coefficient. Beta = standardized regression coefficient. QOL= Quality of Life, AEs = Adverse Events. [*]Statistical significance was concluded at the 2-sided significance level of ≤.05 for these results.

previously [3], the most commonly reported AEs by clinicians were hot flushes (45%) and fatigue (36.4%), whereas common AEs reported by patients were sexual problems, hot flashes and fatigue (all > 70%). Mean cumulative toxicity scores reported by patients were all significantly higher than mean scores reported by clinicians (all *p*'s ≤0.001, Table 3). Cumulative toxicity assessed with the all-grade and severity score showed significant but poor agreement between patients and clinicians (ICC's ≤0.50).

Is cumulative toxicity comprising all grades AEs more associated with QOL than cumulative toxicity comprising high-grade AEs only?

A higher total number of all grades AEs (B=-2.22, 95%CI=-3.32;-1.11, p=≤0.001) and a higher severity score (B=-1.45, 95%CI=-2.18;-0.71, p=≤0.001) reported by clinicians were significantly associated with lower physical QOL (Table 4). The cumulative toxicity score measured by the total of only high-grade AEs did not reach the standard level of statistical significance. None of the cumulative toxicity scores were associated with global QOL (Table 4). All patient-reported cumulative toxicity scores were significantly associated with lower global and physical QOL (all *p*≤0.001)(Table 4). The standardized regression coefficients showed that both the all-grade (Beta=- 0.43, 95%CI=-0.5;-0.3) and severity score (Beta=-0.42, 95%CI=-0.5;-0.3) were more associated with global QOL than the high grade score (Beta=-0.33, 95%CI=-0.4;-0.2) (Table 4). The same pattern was observed for physical QOL: the all-grade (Beta=-0.45, 95%CI=-0.6;-0.3) and severity score (Beta=-0.48, 95%CI=-0.6;-0.4) were more associated with physical QOL) than the high grade score (Beta=- 0.36, 95%CI=-0.5;-0.3) (Table 4).

Is patient-reported cumulative toxicity more associated with QOL than clinician-reported cumulative toxicity?

Patient-reported cumulative toxicity was associated with global QOL regardless of the toxicity measure (all-grade; B=-2.61, 95%CI=-3.31;-1.91, high-grade; B=-2.81, 95%CI=-3.65;-1.97, or severity score; B=-0.91, 95%CI=-1.14;-0.68), whereas clinician-reported cumulative toxicity was not (all *p*>0.05) (Table 4).

With regard to physical QOL, the patient-reported all-grade score (Beta=-0.45, 95%CI=-0.6;-0.3) and severity score (Beta=-0.48, 95%CI=-0.6;-0.4) showed stronger associations than clinician-reported all-grade (Beta=-0.24, 95%CI=-0.4;-0.1) and severity score (Beta=-0.22, 95%CI=-0.34;-0.11). For the high-grades score, the clinician-reported score was not significantly associated with physical QOL, while the patient-reported score was (B=-2.39, 95%CI=-3.13;-1.66) (Table 4).

Discussion

The first objective of this study was to determine whether cumulative toxicity comprising all grades AEs (including low-grade) was more associated with QOL than cumulative toxicity comprising high grade AEs only. In the current analyses in patients with mCNPC we found support for our hypothesis that cumulative toxicity scores comprising all grades AEs reported by the clinician were associated with lower physical QOL. All patient-reported cumulative toxicity measures, including the high-grade score, were associated with lower global and physical QOL. The standardized regression coefficients demonstrated the strongest associations for the all grades and severity scores. We also found support for our second hypothesis that all patient-reported scores were more associated with QOL outcomes than clinician-reported toxicity scores.

These findings indicate that the evaluation of toxicity in patients with metastatic cancer undergoing systemic treatment could be improved in two ways. First, if the assessment of AEs is clinician-based, cumulative toxicity scores comprising all grades AEs (that is including the low grades) are to be preferred over cumulative toxicity scores comprising high-grade AEs only. Second, patient-reported cumulative toxicity scores are to be preferred over clinician-based toxicity scores regarding their impact on QOL. The significance of patient-reported outcomes in symptom assessment has been demonstrated before[21,22], and recently the use of patient-reported outcomes in symptom monitoring in patients with metastatic cancer was shown to be associated with increased survival compared with usual care[23]. In line with previous studies[24,25], our results demonstrated that cumulative AE scores reported by patients compared to those reported by clinicians were more strongly correlated with (all) QOL scores.

Our study should be interpreted in the context of the following considerations. First, although patients and clinicians assessed the same symptoms they did not complete identical questionnaires. This could partially explain the discordance between patients' and clinicians' evaluation in presence and grading of AEs. In addition, symptoms that were not mentioned by clinicians were considered absent. This could have been a source of inaccuracy, because clinicians may not have asked about certain symptoms and therefore may not have included them, which does not mean they were not actually present. Second, the symptom questionnaire for patients has not been formally validated. Yet, it has been used multiple times before and a high agreement between the scoring of identical AEs on the EORTC QLQ-C30 has been shown[3,13]. Third, there was a substantial

proportion of missing data which in general is a major concern halting the routine incorporation of patient-reported outcomes in RCTs. Often, substantial numbers of patients do not have complete patient-reported data due to discontinuation of treatment or progression of disease[26], which is a potential confounding factor especially when evaluating toxicity. Indeed, as reported previously[3], in this study about half of the 385 patients included in the GETUG-trial completed the QOL assessments at baseline and after 3 months of treatment, which could have led to rise to a risk of bias in our study results. Still the combined participation rates of patient-reported AEs and QOL data are comparable with other clinical RCTs assessing QOL in patients with cancer[27]. In addition, clinical characteristics of patients with complete QOL assessments did not significantly differ from patients who did not complete QOL assessments, suggesting that this study population was a representative sample of the GETUG-trial. Fourth, this study included patients with mCNPC of whom only half received chemotherapy and degree of the reported toxicity in general was modest[28]. This may affect the generalizability of the results to patients with other tumor types, treatments, and treatment toxicities. More specifically, clinicians only reported high-grade AEs in a low proportion of patients (in 10.4% and 20% after 3 and 6 months, respectively). While there was no significant association between clinician-reported high-grade cumulative toxicity scores with global and physical QOL, this could have been the result of lack of power instead of lack of effect. However, in our previous study conducted in patients with metastatic colorectal cancer (mCRC), with higher rates of clinician-reported grade 3-4 AEs, a similar lack of effect of clinician-reported high-grade cumulative toxicity on QOL was observed during palliative systemic treatment[8].

Future prospective studies are needed to improve toxicity and QOL evaluation thereby addressing the limitations mentioned here. These should ensure the use of reliable instruments to assess toxicity, such as the CTCAE for clinicians and the recently validated PRO-CTCAE instrument for patients[11], combined with the global QOL and physical functioning subscales of the well-known EORTC-QLQ C30 or FACT questionnaire to assess QOL. Also, when assessing both toxicity and QOL assessments in patients, one should be cautious in timing these assessments, thereby preventing the risk of priming of certain overlapping questions. In addition, the use of electronic collection of patient-reported data is encouraged, since this has been shown to improve compliance rate in several studies[29,30]. Further, even though we have seen that the impact of cumulative toxicity comprising all grades AEs on QOL in patients with mCRC was similar to the impact seen here in patients with mCNPC, this still has to be studied in patients with other stages and types of treatments as well.

A major strength of this paper is that the data obtained from clinicians and patients were collected prospectively at multiple time-points. In contrast, most previous studies reporting on patient-reported (toxicity) measures used cross-sectional data[31,32]. Further, we included a large sample and a homogeneous group of patients that participated in a multicenter trial. Finally, we provided a solid basis for improving future reporting of toxicity by offering a new set of tools consisting of patient self-reported cumulative toxicity scores that correlate well with patients' QOL.

In conclusion, the standard methods for reporting on AEs during systemic treatment that mainly relies on clinician-reported high-grade AEs, could be questioned. We proposed an alternative approach for handling toxicity data. Clinician-based cumulative toxicity scores comprising all grades AEs provide a better measure of treatment burden than toxicity score comprising high-grade AEs only. To assess the impact of toxicity on QOL, patient-based cumulative toxicity scores are to be preferred.

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