Impact of Patient- and Clinician-Reported Cumulative Toxicity on Quality of Life in Patients With Metastatic Castration-Naïve Prostate Cancer

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**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 of patients’ treatment experiences. This study aimed to determine whether cumulative toxicity comprising all-grade 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 castration-naïve prostate cancer participating in the phase III GETUG-AFU 15 trial completed questionnaires on AEs (at 3 and 6 months) and QoL (at baseline and 3 and 6 months). Clinicians reported AEs during clinical visits. Cumulative toxicity scores were calculated for clinicians and patients in 3 ways: total number of high-grade AEs, total number of all-grade AEs, and total number of all AEs multiplied by their grade (severity score). Relationships between cumulative toxicity scores and QoL were studied using longitudinal regression analyses; unstandardized (B) and standardized regression coefficients (\( \beta \)) are reported. **Results:** Of 385 patients, 184 with complete QoL and toxicity data were included. Clinician-reported all-grade AEs (B, –2.2; 95% CI, –3.3 to –1.1; \( P<.01 \)) and severity score (B, –1.4; 95% CI, –2.2 to –0.7; \( P<.01 \)) were associated with deteriorated physical and global QoL, whereas the total number of high-grade AEs was not. All patient-reported scores were significantly (\( P<.01 \) for all) associated with 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 AEs and severity cumulative toxicity scores. **Conclusions:** Patient- and clinician-based cumulative toxicity scores comprising all-grade AEs better reflect impact on patient QoL than toxicity scores comprising high-grade AEs only. To assess the effect of toxicity on QoL, patient-reported cumulative toxicity scores are preferred.

In daily oncology practice, clinicians constantly weigh the expected benefit of treatment against exposure to possible treatment-related adverse events (AEs). 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 patient quality of life (QoL) are important. Providing a representative overview of treatment-related AEs is essential for patients to make an informed decision to undergo treatment.

Currently, the main source of information on toxicity in randomized controlled trials (RCTs) is a clinician-based assessment of AEs during clinic visits using the NCI Common Terminology Criteria for Adverse Events (CTCAE). However, this may be suboptimal, because the reporting of AEs in RCTs is primarily focused on high-grade AEs (grades 3–4), whereas the lower-grade AEs are not always incorporated. Although a description of high-grade toxicities is important and relevant to determine drug safety, patient QoL is also likely to be influenced by the often daily (re)occurring, longer-lasting grade 1 or 2 AEs throughout therapy, because these determine drug tolerability. We recently studied the burden of cumulative toxicity in patients with colorectal cancer (CRC) and found that cumulative toxicity scores comprising all-grade AEs were associated with patients’ physical QoL, whereas the total score of high-grade AEs was not. 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. Symptomatic AEs associated with anticancer treatments seem to be underreported by clinicians and when data are prospectively collected within RCTs, Patient-reported outcomes to assess AEs may provide an alternative measure for patients’ treatment experiences.

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

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

Patients
A total of 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 before and 3 or 6 months after the start of treatment, and for whom patient- and clinician-reported toxicity data were available.

Study Design and Measurements
Patients completed QoL questionnaires at baseline (before 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 ADT + docetaxel group and every 3 months in the ADT-alone group. Patients 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 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 (using a 4-point Likert scale ranging from 1 = not at all; 4 = very much).
CTCAE items representing single AEs were graded on a 4-point Likert scale (1 = mild; 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 absent. Following the approach from our previous study,7 physical function and global QoL were assessed with subscales of the EORTC Quality of Life Questionnaire-Core 30 (EORTC QLQ-C30); this cancer-specific QoL questionnaire is internationally validated and widely used.13 A change in QoL of at least 10 points is regarded as a minimal clinically important difference.15,16 Additionally, patient demographic, tumor, and treatment characteristics and ECOG performance status (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. Multivariable logistic regression analyses were used to compare characteristics of patients from the GETUG-AFU 15 trial who were included in the current analyses versus those who were excluded, and to compare characteristics of patients with missing data versus those with intact data. Prevalence of the specific types of CTCAE grade AEs was calculated. For each patient, we calculated the clinician-based cumulative toxicity scores in 3 ways: (1) high-grade cumulative toxicity score as the total number of severe AEs (grades 3–4), (2) all-grade cumulative toxicity score as the total number of AEs (all grades), and (3) cumulative toxicity severity 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 to 4, analogous to the rating of subjective disturbance. When symptoms were absent, they were coded as 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 (ICCs) were calculated using two-way random-effects models.17 ICC values <0.5 indicate poor agreement, between 0.5 and 0.75 are moderate, between 0.75 and 0.9 are good, and >0.9 are 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- and patient-reported cumulative toxicity scores. In the multivariate regression models, we adjusted for the following covariates: age, ECOG PS, progression during treatment (yes/no), baseline QoL, allocation to treatment arm in the GETUG-AFU 15 trial, metastatic volume (high vs low, with high metastatic volume defined as the presence of visceral metastases and/or at least 4 bone lesions, including at least 1 bone structure beyond the spine or pelvis),19 serum concentration of prostate-specific antigen at treatment initiation (<65 or ≥65 ng/mL), and Gleason score at baseline (2–6 vs 7 vs 8–10).

Unstandardized (B) and standardized regression coefficients (β) and 95% CIs were reported, allowing clinical interpretation (B) and direct comparison (β) of the obtained regression coefficients in the different models, respectively. The standardized regression coefficients were determined by performing the LMM on the QoL and toxicity data after converting these data into Z scores.20 For all statistical analyses, P<.05 was considered statistically significant. Data were analyzed using SPSS Statistics, version 22 (SPSS Inc.).

Results

Patient characteristics of the GETUG-AFU 15 trial are presented in Table 1. Of the 385 patients enrolled, 201 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. No significant differences in baseline demographic and clinical characteristics were seen between the 184 patients included and the 201 patients excluded from the analyses (Table 1). Cumulative clinician-reported scores were avail-
able for 183 (99.5%) and 120 (65.2%) patients at 3 and 6 months after treatment initiation, respectively (Table 2). Additionally, 168 patients (91.3%) completed the patient-reported AEs at 3 months after start of treatment, and 107 patients (58.2%) at 6 months after start of treatment (Table 2). Data were missing for ≥1 QoL or toxicity assessment for 100 patients. Patients with missing values were more likely to have been allocated to the intervention (ADT + docetaxel) arm (68% vs 44%) and to have had progressive disease (12% vs 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 PS of 0 before start of treatment. Mean QLQ-C30 global QoL score 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=.041). Mean QLQ-C30 physical functioning score reduced significantly over time, from 87.2 (16.6) at baseline to 83.4 (18.0) at 3 months and 79.3 (18.8) at 6 months after start of treatment (P≤.001).

### Reporting of AEs and Cumulative Toxicity Scores
Clinicians reported AEs for 159 (86.9%) and 108 (90%) patients between the first 3 months and between 3 and 6 months after start of treatment, respectively. At least one high-grade AE (grade 3–4) was reported in 19 patients (10.4%) during the first 3 months of treatment, and in 24 (20%) between 3 and 6 months (Table 2). All patients reported AEs between the first 3 months and between 3 and 6 months after start of treatment. In total, at least one high-grade AE (grade 3–4) was reported by 149 patients (88.7%) after 3 months of treatment and by 93

### Table 1. Clinical Characteristics of the Study Population

<table>
<thead>
<tr>
<th>GETUG-AFU 15 (N=385)</th>
<th>Excluded From Cumulative AE Study (N=201)</th>
<th>Included in Cumulative AE Study (N=184)</th>
<th>P Value</th>
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<tr>
<td>Age, y</td>
<td>Mean (SD)</td>
<td>Range</td>
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<tr>
<td></td>
<td>63 (7.8)</td>
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<td>Metastatic extent, n (%)</td>
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<td></td>
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<tr>
<td>High-volume disease</td>
<td>183 (47.2%)</td>
<td>96 (47.8%)</td>
<td>87 (47.3%)</td>
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<tr>
<td>Low-volume disease</td>
<td>202 (52.5%)</td>
<td>105 (52.2%)</td>
<td>97 (52.7%)</td>
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<td>Treatment arm, n (%)</td>
<td>ADT + docetaxel</td>
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<td>ADT</td>
<td>194 (50.4%)</td>
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<td>2–6</td>
<td>32 (8.3%)</td>
<td>13 (6.5%)</td>
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<td>6 (3.0%)</td>
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Abbreviations: ADT, androgen deprivation therapy; AE, adverse event; QLQ-C30, Quality of Life Questionnaire Core-30; QoL, quality of life.
Predictive Value of Cumulative Toxicity

Figure 1. Study flow chart.
Abbreviations: ADT, androgen deprivation therapy; QoL, quality of life.
*aComplete assessment defined as follows: QoL: baseline and ≥1 follow-up measurement; clinician-reported toxicity: ≥1 measurement; patient-reported toxicity: ≥1 measurement.

(86.9%) after 6 months of treatment (Table 2). As reported previously, the most commonly reported AEs by clinicians were hot flushes (45%) and fatigue (36.4%), whereas those commonly reported by patients were sexual problems, hot flushes, and fatigue (all >70%). Mean cumulative toxicity scores reported by patients were all significantly higher than mean scores reported by clinicians (P ≤ .001 for all; Table 3). Cumulative toxicity assessed with all-grade AEs and severity score showed significant but poor agreement between patients and clinicians (ICCs ≤ 0.50).

Association Between QoL and Cumulative Toxicity Comprising All-Grade Versus High-Grade AEs: A higher total number of all-grade AEs (B, −2.22; 95% CI, −3.32 to −1.11; P ≤ .001) and a higher severity score (B, −1.45; 95% CI, −2.18 to −0.71; P ≤ .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 (all P > .05; Table 4). The same pattern was observed for physical QoL: all-grade (B, −0.45; 95% CI, −0.6 to −0.3) and severity scores (B, −0.48; 95% CI, −0.6 to −0.4) were more associated with physical QoL than the high-grade score (B, −0.36; 95% CI, −0.5 to −0.3; Table 4).

Association Between QoL and Patient-Reported Versus Clinician-Reported Cumulative Toxicity: Patient-reported cumulative toxicity was associated with global QoL, regardless of the toxicity measure (all-grade score: B, −2.61; 95% CI, −3.31 to −1.91; high-grade score: B, −2.81; 95% CI, −3.65 to −1.97; severity score: B, −0.91; 95% CI, −1.14 to −0.68), whereas clinician-reported cumulative toxicity was not (all P > .05; Table 4). With regard to physical QoL, the patient-reported all-grade score (B, −0.45; 95% CI, −0.57 to −0.32) and severity score (B, −0.48; 95% CI, −0.59 to −0.36) showed stronger associations than clinician-reported all-grade score (B, −0.24; 95% CI, −0.35 to −0.12) and severity score (B, −0.22; 95% CI, −0.34 to −0.11). For high-grade scores, the clinician-reported score was not significantly associated with physical QoL, whereas the patient-reported score was (B, −2.39; 95% CI, −3.13 to −1.66; Table 4).
Discussion

The first objective of this study was to determine whether cumulative toxicity comprising all-grade AEs (including low-grade) was more associated with QoL than cumulative toxicity comprising high-grade AEs only. In the current analysis of patients with mCNPC, we found support for our hypothesis that cumulative toxicity scores comprising all-grade AEs reported by clinicians 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-grade and severity scores. We also found support for our second hypothesis that all patient-reported toxicity scores were more associated with QoL outcomes than clinician-reported.

These findings indicate that the evaluation of toxicity in patients with metastatic cancer undergoing systemic treatment could be improved in 2 ways. First, if the assessment of AEs is clinician-based, cumulative toxicity scores comprising all-grade AEs (ie, including low-grade) 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 previously, and recently the use of patient-reported outcomes in symptom monitoring among patients with metastatic cancer was shown to be associated with increased survival compared with usual care. In line with previous studies, our results demonstrated that cumulative AE scores reported by patients were more strongly correlated with (all) QoL scores than those reported by clinicians.

Our study should be interpreted in the context of several 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 regarding the 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 previously and a high agreement between the scoring of identical AEs on the EORTC QLQ-C30 has been shown. Third, there was a substantial proportion of missing data, which in general is a major concern preventing 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 disease progression, which is a potential confounding factor especially when evaluating toxicity. As reported previously, approximately half of the 385 patients included in the GETUG-AFU 15 trial completed the QoL assessments at baseline and after 3 months of treatment, which could have led 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. In addition, clinical character-
Predictive Value of Cumulative Toxicity

Future prospective studies are needed to improve toxicity and QoL evaluation, thereby addressing the limitations of our study. 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, combined with the global QoL and physical functioning subscales of the well-known EORTC-QLQ C30 or Functional Assessment of Cancer Therapy (FACT) questionnaire to assess QoL. Additionally, when assessing both toxicity and QoL in patients, one should be cautious in timing these assessments, thereby preventing the risk of priming certain overlapping questions. Furthermore, electronic collection of patient-reported data is encouraged, because this has been shown to improve compliance rate in several studies. Lastly, though we have seen that the impact of cumulative toxicity comprising all-grade AEs on QoL in patients with metastatic CRC was similar to the impact seen here in patients with mCNPC, this still must be studied in patients with other cancer stages and treatment types.

A major strength of this study 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. Furthermore, 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.

Conclusions

The standard methods for reporting on AEs during systemic treatment, which mainly rely 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-grade AEs provide a better measure of treatment burden than toxicity scores comprising high-grade AEs only. To assess the impact of toxicity on QoL, patient-based cumulative toxicity scores should be preferred.
References


