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ORIGINAL ARTICLE

ADOPTION OF PATIENT-REPORTED OUTCOMES IN CLINICAL PRACTICE FOR OLDER PATIENTS RECEIVING ACTIVE ANTI-CANCER TREATMENT: IMPACT ON HEALTH-RELATED QUALITY OF LIFE

C. Zichi[1,2], F. De Vita[1,2], J. Paparo[1,2], F. Salerno[1,2], D. Marino[1], E. Sperti[1], G. Lacidogna[1], F. Vignani[1], R. Dionisio[1], C. Baratelli[1,2*], C. G. C. Turco[1,2], D. Ballaminut[1], A. Bellezza[1], P. Chiotto[1], G. Ciriolo[1], R. Comite[1], F. Codegone[1], S. Florio[1], L. Fusco[1], L. Polimeno[1], D. Pozzi[1], E. Zilio[1], V. Ariu[1], S. Terzolo[1], M. Di Maio[1,2]

[1] Division of Medical Oncology, Ordine Mauriziano Hospital, Turin, Italy
[2] Department of Oncology, School of Medicine, University of Turin, Turin, Italy
*Present address: Division of Medical Oncology, San Luigi Gonzaga Hospital, Orbassano, Turin, Italy

CORRESPONDING AUTHOR:

Massimo Di Maio
Department of Oncology, School of Medicine, University of Turin
Division of Medical Oncology, Ordine Mauriziano Hospital
via Magellano 1
10128 Turin, Italy
E-mail: massimo.dimaio@unito.it
ORCID: 0000-0001-8906-3785

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ABSTRACT

In 2018, we introduced a paper-based questionnaire for the assessment of patient-reported symptoms and toxicities in the management of patients receiving active anti-cancer treatment, showing a significant quality of life (QoL) improvement compared to the previous routine practice. In this secondary analysis, we show the results obtained in patients older than 70 years.

Patients treated in 2017 underwent "usual" visits (group A) while patients treated in 2018, before each visit, received a questionnaire by a nurse, in order to provide information to be discussed during the visit (group B). Primary objective was the comparison of QoL changes, measured by EORTC QLQ-C30.

Out of 211 patients, 88 were older than 70 years. Tumors and setting were similar between group A and B. After 1 month, global QoL was improved in group B (mean change from baseline + 4.47 *vs* - 0.89 in group A, p = 0.006, effect size 0.23). There were statistically significant differences, in favor of group B, also for role functioning and emotional functioning. Mean changes from baseline for pain were significantly better for group B (- 3.25 *vs* + 6.03, p = 0.01, effect size 0.43). The proportion of older patients obtaining a clinically significant improvement in global QoL was 36.6% in group B *vs* 19.1% in group A (p = 0.09), without significant heterogeneity in the proportion of patients with improved QoL between younger and older patients (p = 0.60).

The use of patient-reported outcomes in clinical practice for patients receiving active anti-cancer treatment is associated with a significant QoL improvement also in older patients.

KEY WORDS

Patient-reported outcomes; cancer; health-related quality of life; older patients; symptom reporting.

IMPACT STATEMENT

The adoption of paper-based patient-reported outcome measures in clinical practice is associated with a significant QoL improvement in older patients receiving active anti-cancer treatment.

INTRODUCTION

Patient reported outcomes (PROs) are considered the gold standard to describe subjective symptoms of patients with cancer, and their adoption in clinical practice may improve patients' experience and outcomes of care (1). PROs allow to monitor patient's health condition by using information that comes directly from the patient (2). Self-reporting is able to reduce the underestimation of the incidence and the entity of symptoms (3, 4). Several studies have repeatedly demonstrated the importance of PROs in clinical practice, including the seminal randomized controlled trial by Basch and colleagues (5). In that study, the authors proved that, in patients receiving routine chemotherapy for advanced solid tumors, web-based symptoms reporting with automated e-mail alerts resulted in a better health-related quality of life (QoL) at 6 months compared with baseline, fewer emergency room visits, fewer hospitalizations and superior survival.

As a general rule, attention to patients' QoL is particularly important in older subjects, who are usually characterized by more comorbidities, more complex medical histories and increased risk of treatment toxicity. Part of the geriatric population with cancer might be less willing to sacrifice their short-term health condition for the possibility of longer survival (6, 7). One important question for any intervention adopted in cancer clinical practice is its feasibility in older patients, and the reproducibility of the results in this special population compared to their younger counterparts.

In order to improve clinical management of outpatients receiving active anti-cancer treatment at Medical Oncology, Mauriziano Hospital, Turin, Italy, in January 2018 we introduced in routine clinical practice a systematic, patient-reported assessment of symptoms and toxicities (8). We demonstrated that use of PROs in clinical practice was associated with a significant QoL improvement, compared to the traditional visit. In that study we enrolled 229 patients receiving an active anti-cancer treatment between November 2017 and June 2018: patients visited in 2017 were followed according to the standard modality (only medical evaluation), while patients visited in 2018 received, in addition, a paper-based questionnaire allowing the report of symptoms and toxicity, to be discussed during the visit. Global QoL was significantly improved in patients receiving the questionnaire compared to the control group, with significantly better mean changes for fatigue, pain, and appetite loss.

The same dataset was used to describe the concordance between physicians and patients in the description of symptoms (9). We demonstrated that, compared to the usual visit, use of PROs was able to reduce the under-reporting of symptoms by clinicians in patients' health records, although the agreement remained largely suboptimal.

In this secondary, *post hoc* analysis, we present the results obtained in the subgroup of older patients (> 70 years) with the introduction of PROs in clinical practice, both in terms of impact on patients' health related QoL, and in terms of improvement in symptom reporting by clinicians.

MATERIALS AND METHODS

Patients and procedures

The primary analysis included patients treated with an active anti-cancer treatment, as outpatients, at

the Day Hospital of the Division of Medical Oncology, Mauriziano Hospital in Turin, Italy. Patients had received at least one administration of therapy at the time of the first evaluation. Patients included in the control group (who were treated in 2017) underwent only "usual" medical visits, while to patients treated in 2018 a dedicated nurse administered before each visit a specifically designed questionnaire, in order to estimate symptoms and toxicities.

With the aim of describing QoL changes, all patients received two EORTC QLQ-C30 questionnaires: the second was scheduled approximately one month after the first. All patients signed a written consent before filling questionnaires.

Primary objective of our study was the comparison between the two patients' groups in terms of QoL changes, in order to verify if the patient-based assessment of toxicities and symptoms by nurses could significantly improve patients' QoL (8). A secondary analysis described the agreement between patients' and physicians' reports and the rate of possible under-reporting by physicians (9).

Questionnaires

Patient-reported collection of symptoms and toxicities was based on the adoption of a dedicated paper questionnaire. Details of the questionnaire have been previously described (8). In brief, the questionnaire contains 13 questions, corresponding to 13 symptoms/toxicities (mouth problems, nausea, vomiting, constipation, diarrhea, dyspnea, skin problems, nail problems, itching, hand/foot problems, fatigue, pain, other issues). Patients were asked to refer to the period elapsed since previous therapy, and a final question interrogated about the persistence of problems at the moment of the visit. Both groups received two EORTC QLQ-C30 questionnaires (10). According to EORTC QLQ-C30 scoring manual, scores for multi-item scales are calculated by deriving mean raw scores of single items and transforming them linearly into scales ranging from 0 to 100 (11). For single items, only linear transformation is performed. For functional subscales and global health status, higher values represent better function. For symptom scales, higher values represent greater severity of symptoms.

Statistical issues

The sample size for the primary analysis was calculated to detect an effect size of 0.50 between groups in terms of mean changes of global QoL.

For each domain or symptom, mean changes within groups from baseline to the follow-up assessment were reported. A positive value represents an improvement in functional scales, and a worsening in symptom scales. Only patients with available values at baseline and at follow-up assessment were included in the analysis. Differences from baseline scores were compared between groups by a multivariable linear regression model, using baseline values as covariates. QoL response from baseline was derived for global QoL scores as follows: a change of at least 10 points from baseline was defined as clinically relevant (12); patients were considered improved if they reported a score of 10 or more points better than baseline, and were considered worsened if they reported a score of 10 or more points worse than baseline. Patients whose scores changed less than 10 points were considered stable.

Agreement between patient and physician evaluations was assessed by Cohen's (13). Although there is no universal definition of the interpretation of κ values, according to Fleiss, κ values < 0.40 can be interpreted as poor agreement, values between 0.40 and 0.75 as moderate to good agreement, and values > 0.75 as excellent agreement (14). Under-reporting was calculated as the rate of cycles where physicians did not report the symptom in the medical record, out of cycles where patients reported any severity of the symptom in the QoL questionnaire (3). Under-reporting was compared between group A and group B by chi-square test. All statistical tests were two-tailed and p-values less than 0.05 were considered statistically significant. Because of the exploratory nature of the analysis, adjustment for multiple item comparisons was not performed. Analyses were performed with SPSS for Windows, version 26.0.

RESULTS

Out of the 211 patients included in the primary analysis, who received an active anti-cancer treatment between November 2017 and June 2018, 88 were older than 70 years. Namely, 47 patients were visited, in 2017, according to the standard modality (only medical evaluation) (group A) and 41 patients were visited, in 2018, adding the patient-based assessment of toxicity (group B).

Main characteristics of the 2 groups are detailed in **table I**. The majority of patients were males (61.4% and 63.8% in group A and group B, respectively) and median age was 76 years in both groups. The two groups were similar in terms of type of tumor (the

two most common tumors, in both groups, were colorectal and lung cancer) and in terms of type of treatment (90% of patients were treated with chemotherapy). The proportion of patients receiving a second- or further-line treatment was similar.
Older patients were comparable to younger patients in terms of baseline QoL scores: mean baseline global QoL score was 59.96 (standard deviation 21.88) and 57.39 (standard deviation 21.94) in younger and older patients, respectively (**table II**). Among the 2 groups of older patients, there were some statistically significant differences in baseline values favouring group B, including cognitive functioning, social functioning, fatigue, nausea-vomiting and dyspnea. Mean baseline global QoL score was 53.90 (standard deviation 20.84) in group A and 61.38 (standard deviation 22.73) in group B (Wilcoxon test p = 0.06).
Mean changes from baseline of all QoL domains are displayed in **figure 1**. Global QoL was significantly improved in older patients receiving the questionnaire about symptoms and toxicity compared to the control group. Namely, mean change from baseline of global QoL was - 0.89 (standard error 3.54) in group A and + 4.47 (standard error 3.28) in group B (p = 0.006, effect size 0.23). As for the functioning scales, there were statistically significant differences in mean changes from baseline, in favour of group B, for role functioning (- 5.67 in

	GROUP A	GROUP B	WHOLE SERIES
Number of subjects	47	41	88
Gender			
Males	30 (61.4%)	24 (63.8%)	54 (58.5%)
Females	17 (38.6%)	17 (36.2%)	34 (41.5%)
Age			
Median (range)	76 (70-84)	76 (70-82)	76 (70-84)
Type of primary tumor			
Colorectal cancer	14 (29.8%)	8 (19.5%)	22 (25.0%)
Lung cancer	12 (25.5%)	8 (19.5%)	20 (22.7%)
Pancreatic cancer	5 (10.6%)	10 (24.4%)	15 (17.0%)
Genitourinary cancer	7 (14.9%)	5 (12.2%)	12 (13.6%)
Liver / biliary cancer	3 (6.4%)	2 (4.9%)	5 (5.7%)
Mesothelioma	3 (6.4%)	2 (4.9%)	5 (5.7%)
Gastric cancer	2 (4.3%)	2 (4.9%)	4 (4.5%)
Breast cancer	1 (2.1%)	1 (2.4%)	2 (2.3%)
Unknown primary	-	2 (4.9%)	2 (2.3%)
Head & neck cancer	-	1 (2.4%)	1 (1.1%)
Type of anticancer treatment			
Oxaliplatin-or irinotecan-based	15 (31.9%)	9 (22.0%)	24 (27.3%)
Cisplatin-based	9 (19.1%)	7 (17.1%)	16 (18.2%)
Carboplatin-based	4 (8.5%)	3 (7.3%)	7 (8.0%)
Other cytotoxic agents	15 (31.9%)	17 (41.5%)	32 (36.4%)
Immunotherapy	3 (6.4%)	4 (9.8%)	7 (8.0%)
Other drugs	1 (2.1%)	1 (2.4%)	2 (2.3%)
Setting/line of therapy			
Adjuvant therapy	6 (12.8%)	5 (12.2%)	11 (12.5%)
First-line treatment*	30 (63.8%)	30 (73.2%)	60 (68.2%)
Second-line treatment	9 (19.1%)	5 (12.2%)	14 (15.9%)
Third-or fourth-line treatment	2 (4.3%)	1 (2.4%)	3 (3.4%)

Table I. *Main characteristics of the 88 subjects older than 70 years included in the analysis.*
*including neo-adjuvant treatments.

	PATIENTS YOUNGER THAN 70			PATIENTS OLDER THAN 70 YEARS				
	Group A (n = 72)	Group B (n = 51)	All (n = 123)	Group A (n = 47)	Group B (n = 41)	All (n = 88)		
	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	P value (older *vs* younger)	P value (older group A *vs* B)
Global QoL	59.26 (23.22)	60.95 (20.03)	59.96 (21.88)	53.90 (20.84)	61.38 (22.73)	57.39 (21.94)	0.24	0.06
Functional scales								
Physical functioning	80.37 (18.14)	75.42 (20.24)	78.32 (19.12)	72.20 (17.10)	75.77 (23.61)	73.86 (20.35)	0.09	0.07
Role functioning	75.00 (27.69)	66.99 (32.06)	71.68 (29.62)	74.82 (25.03)	81.30 (23.63)	77.84 (24.46)	0.23	0.15
Emotional functioning	78.13 (17.32)	75.98 (23.67)	77.24 (20.13)	74.11 (21.93)	80.89 (17.10)	77.27 (20.00)	0.97	0.18
Cognitive functioning	81.94 (21.07)	85.95 (16.12)	83.60 (19.20)	79.08 (23.43)	91.46 (15.86)	84.85 (21.09)	0.41	0.002
Social functioning	73.61 (28.49)	77.45 (23.05)	75.20 (26.34)	75.89 (23.52)	87.40 (19.64)	81.25 (22.43)	0.12	0.008
Symptoms								
Fatigue	41.36 (21-85)	41.39 (22.34)	41.37 (21.96)	40.43 (17.71)	32.25 (18.89)	36.62 (18.62)	0.10	0.035
Nausea -vomiting	10.65 (17.31)	16.01 (23.08)	12.87 (20.00)	12.41 (17.19)	5.69 (17.32)	9.28 (17.48)	0.08	0.005
Pain	19.91 (24.00)	21.57 (26.73)	20.57 (25.08)	21.63 (24.55)	19.51 (30.02)	20.64 (27.10)	0.73	0.37
Sleeping disturbance	28.24 (29.42)	22.88 (25.38)	26.02 (27.84)	26.95 (29.19)	21.95 (29.45)	24.62 (29.25)	0.59	0.35
Appetite loss	21.30 (27.58)	21.57 (29.68)	21.41 (28.35)	24.11 (26.65)	19.51 (27.86)	21.97 (27.16)	0.75	0.28
Diarrhea	17.13 (26.83)	12.42 (24.91)	15.18 (26.05)	15.60 (27.67)	14.63 (23.63)	15.15 (25.73)	0.94	0.83
Constipation	23.61 (30.35)	28.76 (29.83)	25.75 (30.12)	26.24 (29.44)	23.58 (27.13)	25.00 (28.25)	0.98	0.73
Financial	12.04 (25.82)	14.38 (26.04)	13.01 (25.83)	9.93 (19.55)	7.32 (19.02)	8.71 (19.24)	0.30	0.44
Dyspnea	15.28 (23.02)	16.34 (21.47)	15.72 (22.31)	25.53 (26.20)	15.45 (23.68)	20.83 (25.43)	0.14	0.04

Table II. *Mean baseline quality of life* scores according to patients' age and group.*

*EORTC QLQ-C30 baseline questionnaire.

Group A: patients visited in 2017 with standard approach; Group B: patients visited in 2018 with the use of paper-based questionnaires; SD: standard deviation.

group A and - 0.81 in group B, p = 0.034, effect size 0.20) and emotional functioning (- 2.30 in group A and + 3.25 in group B, p = 0.014, effect size 0.36). As for symptoms, mean changes from baseline in the group of patients receiving the questionnaire about symptoms and toxicity compared to the control group were significantly better for pain. Namely, mean change from baseline was + 6.03 (standard error 2.75) in group A and - 3.25 (standard error 3.74) in group B (p = 0.01, effect size 0.43). There were no significant differences between the two groups in terms of other symptoms.

The proportion of patients obtaining a clinically significant improvement in global QoL score was numerically higher in group B compared to group A: as reported in **figure 2**, an improvement was observed

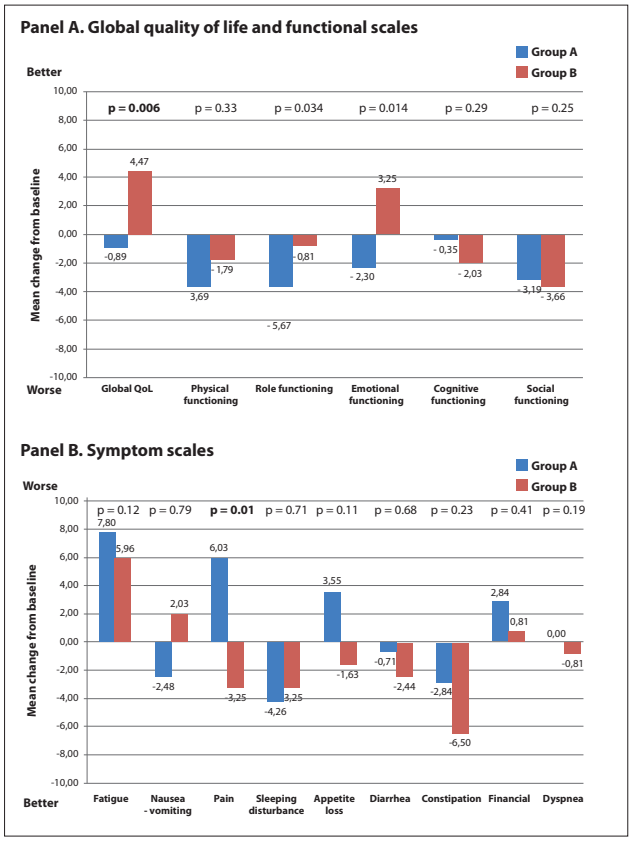

Figure 1. *Mean changes from baseline of all quality of life (QoL) domains.* ***Panel A****: global QoL and functional scales (positive indicates improvement);* ***Panel B****: symptom scales (negative indicates improvement). Blue bars: group A ("usual" medical visit); red bars: group B (medical visit + systematic collection of information about symptoms and toxicities).*

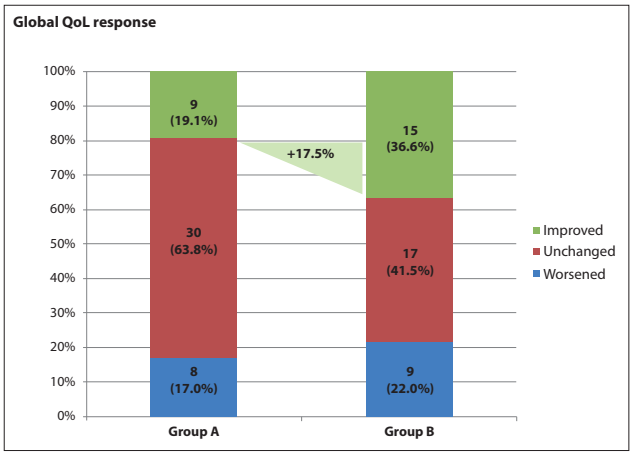

Figure 2. *Proportion of patients with health-related global quality-of-life (QoL) changes at second questionnaire compared with baseline. Patients were considered improved if they reported a score of 10 or more points better than baseline (green bars), and were considered worsened if they reported a score 10 or more points worse than baseline (blue bars). Patients whose scores changed less than 10 points were considered stable (red bars). Group A: patients visited in 2017 with standard approach; Group B: patients visited in 2018 with the use of paper-based questionnaires.*

in 9 patients in group A (19.1%, 95% confidence interval 10.2%-32.8%) and in 15 patients in group B (36.6%, 95% confidence interval 23.6%-51.9%) (p = 0.09). There was no significant heterogeneity in the proportion of QoL responders between younger and older patients (Breslow-Day test for homogeneity, p = 0.597). The Odds Ratio of obtaining an improvement in global QoL fro group B *vs* group A was 1.73 (95% CI 0.75-3.99) in younger patients and 2.44 (95% CI 0.93–6.40) in older patients.

Table III describes the agreement between patients reporting and physician reporting, scattered by group (group A receiving "classic" visit and group B receiving the nurse-administered questionnaire for description of symptoms). For all symptoms, Cohen's κ was better for group B, receiving the nurse-administered questionnaire, compared to group A, receiving "classic visit". In detail, Cohen's κ improved from 0.30 to 0.41 for emesis, from 0.10 to 0.61 for diarrhea, from 0 to 0.20 for constipation, from 0.17 to 0.48 for pain and from 0.01 to 0.10 for fatigue.

As shown in **figure 3**, in the whole series, the proportion of under-reporting by physicians (*i.e.*, patients reported the symptom in the questionnaire, but physicians did not report the symptom in the health record of the visit) was 70.18% for emesis, 68.09% for diarrhea, 89.77% for constipation, 60.00% for pain and 76.77% for fatigue. For all symptoms, however, although under-reporting was numerically relevant in both groups, reporting was improved for group B compared to group A. In detail, under-reporting improved from 73.68% to 63.16% for emesis (p = 0.413), from 88.00% to 45.45% for diarrhea (p = 0.002), from 97.92% to 80.00% for constipation (p = 0.006), from 72.22% to 38.71% for pain (p = 0.002) and from 87.50% to 62.69% for fatigue (p < 0.001). For all symptoms, the overall underreporting was not significantly different between younger and older patients (with the exception of constipation, that was more under-reported in elderly patients), and there was no significant heterogeneity in the improvement in symptom reporting in group B *vs* group A, between younger and older patients.

DISCUSSION

In this secondary, *post hoc* analysis of our experience with adoption of patient-reported outcomes

		EMESIS	DIARRHEA	CONSTIPATION	PAIN	FATIGUE
Group A (receiving usual visit)						
Symptom reported by:	Patient: NO Physician: NO	54 (58.7%)	64 (69.6%)	43 (46.7%)	35 (38.0%)	4 (4.3%)
	Patient: NO Physician: YES	0	3 (3.3%)	1 (1.1%)	3 (3.3%)	0
	Patient: YES Physician: NO	28 (30.4%)	22 (23.9%)	47 (51.1%)	39 (42.4%)	77 (83.7%)
	Patient: YES Physician: YES	10 (10.9%)	3 (3.3%)	1 (1.1%)	15 (16.3%)	11 (12.0%)
	Cohen's κ* (95% CI)	0.30 (0.08-0.51)	0.10 (0–0.40)	0 (0-0.06)	0.17 (0-0.36)	0.01 (0-0.10)
Group B (receiving paper-based questionnaire with patient-reported outcomes)						
Symptom reported by:	Patient: NO Physician: NO	59 (73.8%)	57 (71.3%)	40 (50.0%)	42 (52.5%)	11 (13.8%)
	Patient: NO Physician: YES	2 (2.5%)	1 (1.3%)	0	7 (8.8%)	2 (2.5%)
	Patient: YES Physician: NO	12 (15.0%)	10 (12.5%)	32 (40.0%)	12 (15.0%)	42 (52.5%)
	Patient: YES Physician: YES	7 (8.8%)	12 (15.0%)	8 (10.0%)	19 (23.8%)	25 (31.3%)
	Cohen's κ*	0.41 (0.13-0.69)	0.61 (0.39-0.82)	0.20 (0-0.42)	0.48 (0.28-0.69)	0.10 (0-0.28)

Table III. *Analysis of agreement between patient reporting (any severity) and physician reporting (any grade) of symptoms, according to modality of visit.*

*κ > 0.75: excellent agreement; κ = 0.40-0.75: fair to good agreement; κ < 0.40: poor agreement.

in patients receiving active anticancer treatment in routine clinical practice, we have shown that the adoption of questionnaires in clinical practice is associated with a significant improvement in global QoL also in older subjects.

Older adults represent the majority of patients treated in oncology clinical practice. However, while the number of studies describing the use of PROs in cancer patients has rapidly grown, studies specifically dedicated to PROs use in older patients are much more limited. Considering the peculiar characteristics of older subjects, our aim was to verify if the use of PROs, which has been shown to improve QoL (8), shows a similar benefit also in the population of older patients. Our findings suggest that the results obtained in the whole study population are similar also in the subgroup of older subjects, showing a significant QoL improvement in patients receiving the questionnaires about symptoms and toxicities, compared to the control group.

Notably, in addition to the significant difference in global QoL, we observed a significant benefit in the control of pain. This result in older patients confirmed what our analysis had shown in the whole patients' population (8). As we already discussed in the primary analysis, this improvement in pain control could reasonably play a relevant role in the better global QoL. We believe that a written report of the presence and the intensity of pain, made possible by the administration of questionnaires, could reasonably improve the communication between patients and physicians, favoring a better management of the symptom.

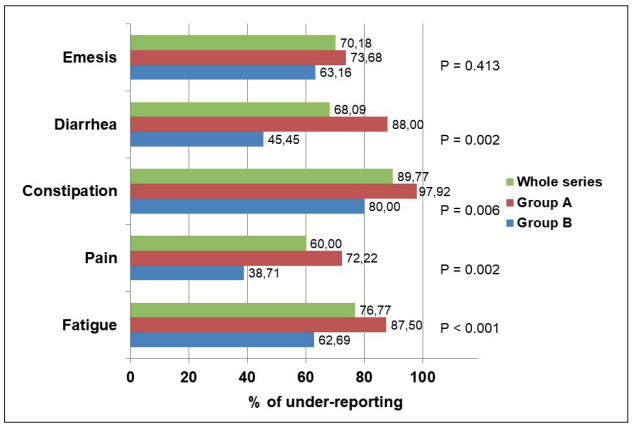

Figure 3. *Proportion of under-reporting for each of the 5 symptoms considered (emesis, diarrhea, constipation, pain, fatigue) in the whole series (green bars), in the **Group A** of patients receiving "usual" visits (red bars), and in the **Group B** of patients receiving questionnaires to report patient-reported outcomes (blue bars).*

In addition to improvements in patient reported health status and quality of life, as already demonstrated in the whole study population (9), this subgroup analysis focused on older patients confirmed that the use of PROs reduces the under-reporting by physicians of symptoms and toxicities, improving the accuracy of the information included in patients' health records.

All the results described in this paper were obtained with the use of "old style", paper-based PROs. There is no doubt that the use of electronic PROs could have important advantages compared to paper-based questionnaires (15). In recent years, several studies have confirmed the feasibility of electronic patient-reporting of symptomatic side effects of cancer treatment, suggesting high acceptability of the procedures and high patients' satisfaction (5, 16-18). While paper-based questionnaires are simply discussed during the hospital visit, use of electronic PROs can offer a real-time reporting and monitoring of symptoms and toxicities, potentially improving the medical management. However, the use of electronic PROs could be potentially more complicated for older patients and those with less confidence with modern technology (19). Older patients might be less able to use tablets, personal computers or other electronic tools. Despite these concerns, in the seminal trial by Basch and colleagues, even those patients who declared to be unexperienced with technology were able to regularly report their symptoms via the web, throughout the course of their anticancer treatment (5). Although older patients did not show the same benefit that was apparent in younger patients in terms of reduction of emergency room visits or survival, no significant interaction with patients' age was demonstrated as for the quality of life improvement and the reduced risk of hospitalizations. Use of electronic instruments will likely increase in the future, and with appropriate education these tools can be used with good compliance also in older patients (20, 21).

Our study presents some limitations. First of all, we did not conduct a randomized comparison, so we cannot exclude some unintended difference between the two groups. However, even considering the subgroup of older patients included in this secondary analysis, the two groups were similar in terms of age, gender, type of tumor and line of treatment. Furthermore, we acknowledge that this subgroup analysis of older patients was not preplanned, and we conducted it *post hoc*, following the positive results obtained in the whole study population, with the aim of specifically producing evidence about the use of PROs in older subjects. As we already discussed in the primary paper, we have used a non-validated instrument for the collection of symptoms and toxicities. Lastly, the QoL improvement was not very large, both in terms of the effect size of the mean difference between groups and in terms of the absolute difference in the proportion of patients experiencing a QoL improvement. However, this result has been obtained with a "low-cost" intervention, so we strongly believe that even a small improvement in QoL for our patients allows to consider the adoption of PROs in clinical practice cost-effective and useful.

In conclusion, this secondary analysis shows that the use of PROs in clinical practice, thanks to an active role of nurses and discussion of symptoms with physicians during the visit, is associated, with a significant improvement in global QoL also in older patients receiving active anticancer treatment.

ETHICS

Fundings

Massimo Di Maio was recipient of a research funding from the CRT Foundation (Turin, Italy) for a project on the impact on quality of life of the systematic evaluation of toxicity with patient-reported outcomes in patients with solid cancer (CRT grant number 46333, "Richieste ordinarie 2015").

Conflicts of interests

Massimo Di Maio received honoraria and had roles as consultant or advisor for AstraZeneca, Pfizer, Novartis, Roche, Takeda, Eisai, Janssen, Astellas; received institutional research grant by Tesaro – GlaxoSmithKline, outside this work. Donatella Marino received honoraria and had roles as advisor for Roche. All remaining authors declared no conflicts of interests.

Availability of data and material

Authors have full control of all primary data and agree to allow the journal to review their data if requested.

Code availability

N/A

Authors' contribution

Study conception and design: MDM. Study conduction and data collection: DM, ES, GL, FV, RD, CB, CGCT, DB, AB, PC, GC, RC, FC, SF, LF, LP, DP, EZ, VA, ST. Data analysis: MDM. Manuscript writing: CZ, FDV, JP, FS, MDM. Manuscript revision for important intellectual content: All authors.

Ethical approval

Questionnaires were submitted as part of routine clinical practice, so no specific approval to Ethics Committee was requested.

Consent to participate

All patients signed a written consent before filling questionnaires.

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