

The association of financial difficulties with clinical outcomes in cancer patients: secondary analysis of 16 academic prospective clinical trials conducted in Italy[†]

F. Perrone^{1*}, C. Jommi², M. Di Maio^{1,‡}, A. Gimigliano¹, C. Gridelli³, S. Pignata⁴, F. Ciardiello⁵, F. Nuzzo⁶, A. de Matteis⁶, L. Del Mastro⁷, J. Bryce¹, G. Daniele¹, A. Morabito⁸, M. C. Piccirillo¹, G. Rocco⁹, L. Guizzaro^{10,11} & C. Gallo¹¹

¹Research Department, Clinical Trial Unit, National Cancer Institute, G.Pascale Foundation – IRCCS, Naples; ²Drug Science Department, University of Piemonte Orientale, Novara, and CERGAS (Centre for Research on Health and Social Care Management), Bocconi University, Milan; ³Department of Oncology/Hematology, Division of Medical Oncology, 'S.G. Moscati' Hospital, Avellino; ⁴Urogynecologic Department, Medical Oncology, National Cancer Institute, G.Pascale Foundation – IRCCS, Naples; ⁵Department of Internal and Experimental Medicine 'F. Magrassi ed A. Lanzara', Division of Medical Oncology, Second University of Naples, Naples; ⁶Senology Department, Medical Oncology, National Cancer Institute, G.Pascale Foundation – IRCCS, Naples; ⁷Department of Medicine, Development of Innovative Treatment Unit, IST National Institute for Cancer Research – IRCCS SanMartino, Genoa; ⁸Departments of Thoracic Medical Oncology; ⁹Thoracic Surgical and Medical Oncology, Division of Thoracic Surgery, National Cancer Institute, G.Pascale Foundation – IRCCS, Naples, Italy; ¹⁰European Medicines Agency, London, UK; ¹¹Department of Mental Health and Preventive Medicine, Medical Statistics, Second University of Naples, Naples, Italy

Received 3 August 2016; revised 2 September 2016; accepted 8 September 2016

Background: Cancer may cause financial difficulties, but its impact in countries with public health systems is unknown. We evaluated the association of financial difficulties with clinical outcomes of cancer patients enrolled in academic clinical trials performed within the Italian public health system.

Patients and methods: Data were pooled from 16 prospective multicentre trials in lung, breast or ovarian cancer, using the EORTC quality of life (QOL) C30 questionnaire. Question 28 scores financial difficulties related to disease or treatment in four categories from 'not at all' to 'very much'. We defined financial burden (FB) as any financial difficulty reported at baseline questionnaire, and financial toxicity (FT) as score worsening in a subsequent questionnaire. We investigated (i) the association of FB with clinical outcomes (survival, global QOL response [questions 29/30] and severe toxicity), and (ii) the association of FT with survival. Multivariable analyses were performed using logistic regression models or the Cox model adjusting for trial, gender, age, region and period of enrolment, baseline global QOL and, where appropriate, FB and global QOL response. Results are reported as odds ratio (OR) or hazard ratio (HR) with 95% confidence intervals (CI).

Results: At baseline 26% of the 3670 study patients reported FB, significantly correlated with worse baseline global QOL. FB was not associated with risks of death (HR 0.94, 95% CI 0.85–1.04, $P = 0.23$) and severe toxicity (OR 0.90, 95% CI 0.76–1.06, $P = 0.19$) but was predictive of a higher chance of worse global QOL response (OR 1.35, 95% CI 1.08–1.70, $P = 0.009$). During treatment, 2735 (74.5%) patients filled in subsequent questionnaires and 616 (22.5%) developed FT that was significantly associated with an increased risk of death (HR 1.20, 95% CI 1.05–1.37, $P = 0.007$). Several sensitivity analyses confirmed these findings.

Conclusion: Even in a public health system, financial difficulties are associated with relevant cancer patients outcomes like QOL and survival.

Clinical Trials number: Any registered clinical trial number should be indicated after the abstract.

Key words: financial toxicity, public health system, quality of life, overall survival

*Correspondence to: Dr Francesco Perrone, Research Department, Clinical Trial Unit, National Cancer Institute, G.Pascale Foundation – IRCCS, via M.Semmola, 80131 Napoli, Italy. Tel: +39-0815903571; Fax: +39-0817702938, E-mail: f.perrone@istitutotumori.na.it

[†]The views expressed in this article are the personal views of the author and may not be understood or quoted as being made on behalf of or reflecting the position of the European Medicines Agency or one of its committees or working parties.

[‡]Present address: Oncology Department, University of Turin, Orbassano, Italy.

introduction

Financial problems are matter of attention in oncology, primarily due to the increasing cost of new drugs, unaffordable by patients in health systems where co-payment is required [1]. However, financial difficulties might occur even in countries where co-payment is not required (e.g. the Macmillan's research report 'Revealing the costs behind the illness' at <http://www.macmillan.org.uk>, accessed

30 August 2016). In Italy, a NHS-based (National Health Service) public health care system exists, and most of the clinical pathway of cancer patients is cost-free, including inpatient and outpatient services and drugs.

There are two levels of financial difficulties, the society level and the patient level. The first is encumbered by the rising cost of new drugs, that is a problem worldwide for both public payers and patients, when co-payment is required [2]. Cancer patients in the United States have higher likelihood to file for bankruptcy than the general population [3]. In turn, financial difficulties have been associated with lower patient satisfaction [4], worse compliance [5], worse quality of life (QOL) [6–8], and worse survival [9].

Provocatively, it has been suggested that financial toxicity might be graded similarly to traditional side effects, to help researchers understand the economic impact of new drugs [10]. Also, it has been suggested that existing tools that measure financial problems should be investigated to understand whether what they measure is associated with patients' outcomes [11].

Question 28 (Q28) of the EORTC QLQ-C30 questionnaire for QOL analysis asks 'During the last week, has your physical condition or medical treatment caused you financial difficulties?' [12]. We have frequently used the EORTC QLQ-C30 questionnaire in clinical trials of treatment of solid tumours and planned to perform a pooled analysis of such trials, to explore whether (i) financial difficulties at baseline are associated with patients' outcomes (survival, QOL and toxicity), and (ii) the development of financial difficulties during treatment is associated with overall survival.

methods

This study is an unplanned secondary analysis performed pooling 16 prospective trials promoted by the National Cancer Institute of Napoli (Italy) between 1996 and 2008 (supplementary Table S1, available at *Annals of Oncology* online). All trials were approved by the Ethics Committees at participating Institutions; their results have already been published (see references in the online supplementary material, available at *Annals of Oncology* online). Out of 162 participating centres, 160 were public institutions, either general or university hospitals or cancer centres; two private centres were under contract with the public system and, similarly, did not require any co-payment from patients.

All patients enrolled in the pooled trials were eligible. Exclusion criteria were (i) having been enrolled outside Italy and (ii) missing response to Q28 at the baseline EORTC QLQ C30 questionnaire.

The EORTC QLQ-C30 questionnaire was administered with varying schedules across trials, according to chemotherapy cycles, from baseline to the end of cycle 6 (supplementary Table S2, available at *Annals of Oncology* online); questionnaires completed on day 8 of cycle 1 (in 5 lung cancer trials) were not taken into account in the present analysis. Response codes to Q28 range from 1 to 4, corresponding to 'not at all', 'a little', 'quite a bit' and 'very much'. For this study, the presence of financial difficulties at the baseline questionnaire and the worsening (or the appearance) of financial difficulties in subsequent questionnaires were coded in different ways. Namely, we called the former 'Financial burden' (FB) and the latter 'Financial toxicity' (FT). Obviously, FT could be measured only among patients who fulfilled at least one questionnaire after the baseline. FB and FT were primarily analysed as binary variables (any grade versus not at all), but three categories were also considered in sensitivity analyses. Responses to questions 29 and 30 range from 1 (the worst score) to 7 (the best score). They were combined

and linearly transformed into the global health status/QOL scale ranging from 0 to 100, hereby defined global QOL [13]. Variability of baseline global QOL according to categories of FB at baseline was tested with the Kruskal–Wallis non parametric ANOVA.

Geographic origin referred to the centres where the patients were enrolled, because birth place and place of residency were not recorded. Patients were clustered according to the enrolment date into three time-windows: 1996–2001, 2002–2006, 2007–2012.

Three outcome variables were evaluated: clinical toxicity, QOL and survival.

Clinical toxicity was measured across the trials with different subsequent editions of internationally accepted criteria: WHO, NCI-CTC version 2, and CTCAE versions 2 and 3. Such variability, however, does not affect intra-trial consistency and should not affect the whole analysis. We calculated the worst grade experienced by each patient over treatment in all toxicity items, grades ranged from 0 (no toxicity) to 5 (toxicity-related death); severe toxicity was defined as grade ≥ 3 . The prognostic role of FB for severe toxicity was reported as odds ratio (OR) with 95% confidence interval (CI) and tested with a logistic model adjusted for gender, age, region, period of enrolment, baseline global QOL and trial.

Global QOL worsening was defined as a decrease of at least 10 points at any time point from baseline without any improvement ≥ 10 points at any time point over baseline [14]. The prognostic role of FB on global QOL worsening was reported as OR with 95% CI and tested with a logistic model adjusted for gender, age, region, period of enrolment, baseline global QOL and trial.

Survival was calculated as the number of months between randomization and the date of death or of last information on vital status. The prognostic role of FB on survival was reported as hazard ratio (HR) of death with 95% CI and tested with a Cox proportional hazard model stratified by trial and adjusted for gender, age, region, period of enrolment and baseline global QOL. To evaluate the role of FT on overall survival a Cox proportional hazard model was used, stratified by trial and adjusted by gender, age, region, period of enrolment, baseline FB, baseline global QOL and global QOL response. To remove the bias due to the time-dependent nature of financial toxicity, a landmark survival analysis was used with a landmark time of 4.5 months (i.e. the maximum planned time to complete all the QLQ-C30 questionnaires); therefore, patients who died or had the last information on vital status before 4.5 months from randomization were excluded.

Because of possible heterogeneity among trials, sensitivity analyses were performed excluding one single trial at a time, one disease (lung or breast or ovary) at a time, and one setting (adjuvant, metastatic) at a time. Further sensitivity analyses were performed for the impact of FT on survival, varying the landmark threshold from 4.5 months up to 24 months.

results

Overall, 4722 patients had been enrolled in 16 trials; 252 patient enrolled outside Italy were excluded and a further 800 were excluded due to missing response to baseline Q28. Therefore, 3670 patients were included in the analysis.

Distribution of baseline characteristics, according to response to baseline Q28 is reported in Table 1. Overall, 956 patients (26.0%) reported at least some grade of FB. A lower percentage of FB was found in Northern Italy, male gender, elderly and earlier recruitment date.

Baseline global QOL significantly ($P < 0.0001$) decreased with greater financial burden (supplementary Figure S1, available at *Annals of Oncology* online).

Results of the models evaluating the prognostic role of FB on clinical outcomes are reported in Table 2. Out of 3670 patients, 2473 (67.4%) died. FB was not significantly associated with the

Table 1. Distribution of patients according to baseline characteristics and baseline financial burden

	Total N = 3670 n	During the last week, has your physical condition or medical treatment caused you financial difficulties?								P
		Not at all N = 2714		A little N = 669		Quite a bit N = 205		Very much N = 82		
		n	(%)	n	(%)	n	(%)	n	(%)	
Trial—type of cancer										<0.001
1. BREAST10—breast	126	83	(65.9%)	27	(21.4%)	11	(8.7%)	5	(4.0%)	
2. CAPP2—NSCLC	37	23	(62.2%)	11	(29.7%)	–		3	(8.1%)	
3. DISTAL—NSCLC	192	124	(64.6%)	47	(24.5%)	15	(7.8%)	6	(3.1%)	
4. DISTAL2—NSCLC	73	39	(53.4%)	18	(24.7%)	10	(13.7%)	6	(8.2%)	
5. EDD—breast	16	6	(37.5%)	4	(25.0%)	3	(18.8%)	3	(18.8%)	
6. ELDA—breast	251	158	(62.9%)	76	(30.3%)	12	(4.8%)	5	(2.0%)	
7. ELVIS—NSCLC	149	119	(79.9%)	24	(16.1%)	6	(4.0%)	–		
8. GECO—NSCLC	358	259	(72.3%)	65	(18.2%)	21	(5.9%)	13	(3.6%)	
9. GEMVIN2—NSCLC	129	94	(72.9%)	23	(17.8%)	10	(7.8%)	2	(1.6%)	
10. GEMVIN3—NSCLC	342	252	(73.7%)	68	(19.9%)	16	(4.7%)	6	(1.8%)	
11. G-STEP—SCLC	62	58	(93.5%)	4	(6.5%)	–		–		
12. MILES—NSCLC	594	506	(85.2%)	66	(11.1%)	17	(2.9%)	5	(0.8%)	
13. MILES2—NSCLC	193	169	(87.6%)	19	(9.8%)	4	(2.1%)	1	(0.5%)	
14. MITO2—ovary	617	402	(65.2%)	147	(23.8%)	54	(8.8%)	14	(2.3%)	
15. TAXw—breast	38	32	(84.2%)	4	(10.5%)	1	(2.6%)	1	(2.6%)	
16. TORCH—NSCLC	493	390	(79.1%)	66	(13.4%)	25	(5.1%)	12	(2.4%)	
Age										<0.001
≤65	1654	1106	(66.9%)	354	(21.4%)	136	(8.2%)	58	(3.5%)	
>65	2016	1608	(79.8%)	315	(15.6%)	69	(3.4%)	24	(1.2%)	
Gender										<0.001
Males	2120	1654	(78.0%)	327	(15.4%)	97	(4.6%)	42	(2.0%)	
Females	1550	1060	(68.4%)	342	(22.1%)	108	(7.0%)	40	(2.6%)	
Region										<0.001
North	956	804	(84.1%)	113	(11.8%)	31	(3.2%)	8	(0.8%)	
Centre	509	343	(67.4%)	109	(21.4%)	41	(8.1%)	16	(3.1%)	
South/islands	2205	1567	(71.1%)	447	(20.3%)	133	(6.0%)	58	(2.6%)	
Period of enrolment										<0.001
1996–2001	1353	1071	(79.2%)	208	(15.4%)	57	(4.2%)	17	(1.3%)	
2002–2006	1456	1028	(70.6%)	293	(20.1%)	97	(6.7%)	38	(2.6%)	
2007–2012	861	615	(71.4%)	168	(19.5%)	51	(5.9%)	27	(3.1%)	

risk of death, with a HR of 0.94 (95% CI 0.85–1.04, $P = 0.23$). Global QOL response was calculated in 2703 (73.7%) patients; of these, 917 (33.9%) worsened QOL without any previous improvement. FB was significantly associated with worsening global QOL (OR 1.35, 95% CI 1.08–1.70, $P = 0.009$). Clinical toxicity data were available for 3573 (97.4%) patients; of these, 1586 (44.4%) had severe clinical toxicity. There was no association between FB and occurrence of severe clinical toxicity (OR 0.90 95% CI 0.76–1.06, $P = 0.19$). Similar results were found when three categories were considered for FB (supplementary Table S3, available at *Annals of Oncology* online). Sensitivity analyses, performed removing trials, or disease or stage of disease, one at a time, substantially confirmed all the previous findings (supplementary Figures S2–S4, available at *Annals of Oncology* online).

Overall, 2735 (74.5%) patients answered Q28 of the QLQ-C30 questionnaire at least once after the baseline. Of these, 58 (2.0%) had reported the worst score (very much) at the baseline questionnaire and by definition could not develop financial toxicity during the treatment; 616 (22.5%) developed financial toxicity

while on treatment (Table 3), ranging from 8.3% to 40.7% across the different clinical trials (supplementary Table S4, available at *Annals of Oncology* online).

Financial toxicity was associated with a statistically significant higher risk of death (HR 1.20, 95% CI 1.05–1.37, $P = 0.007$), when the landmark time of 4.5 months was used. Similar results were found when three categories were considered for FT (supplementary Table S3, available at *Annals of Oncology* online). Results did not vary in sensitivity analyses when landmark threshold was increased (Figure 1) and trials, or disease or stage of disease were removed one at a time (supplementary Figure S5, available at *Annals of Oncology* online).

discussion

We found that in a large series of Italian cancer patients enrolled in clinical trials, about one-quarter had some FB at baseline, and a further 22% developed FT while on treatment. Baseline FB was associated with a clinically relevant worsening of QOL during the treatment, and FT that developed during treatment was

Table 2. Association of financial burden and financial toxicity with clinical outcomes

Variable and outcome	Model	n	Events	Measure	Value	95% CI	P
Baseline financial burden (<i>any grade versus not at all</i>)							
Overall survival	Cox model ^a	3655	2462	HR of death	0.94	0.85–1.04	0.23
Global QoL	Logistic regression ^a	2703	917	OR of worsening	1.35	1.08–1.70	0.009
Clinical toxicity	Logistic regression ^a	3558	1579	OR of grade ≥ 3	0.90	0.76–1.06	0.19
Financial toxicity (≥1-point worsening versus no-worsening)							
Overall survival (4.5 months landmark)	Cox model ^b	2263	1382	HR of death	1.20	1.05–1.37	0.007

HR, hazard ratio; OR, odds ratio.

^aAdjusted by gender, age, period, region, baseline global QOL (15 cases with data missing) and trial.

^bAdjusted by gender, age, period, region, baseline response to Q28, baseline global QOL (15 cases with data missing), global QOL response and trial.

Table 3. Distribution of patients according to responses given to baseline question 28 and the worst response given to question 28 in the subsequent questionnaires

Response to question 28 at baseline	Total n	Worst response to question 28 at subsequent questionnaires							
		Not at all		A little		Quite a bit		Very much	
		n	(%)	n	(%)	n	(%)	n	(%)
Not at all	2015	1540	(76.4%)	358	(17.8%)	91	(4.5%)	26	(1.3%)
A little	508	115	(22.6%)	282	(55.5%)	91	(17.9%)	20	(3.9%)
Quite a bit	154	12	(7.8%)	41	(26.6%)	71	(46.1%)	30	(19.5%)
Very much	58	2	(3.4%)	14	(24.1%)	15	(25.9%)	27	(46.6%)

Bold numbers represent cases who are labelled as any financial toxicity. Grey cell refer to moderate and severe worsening.

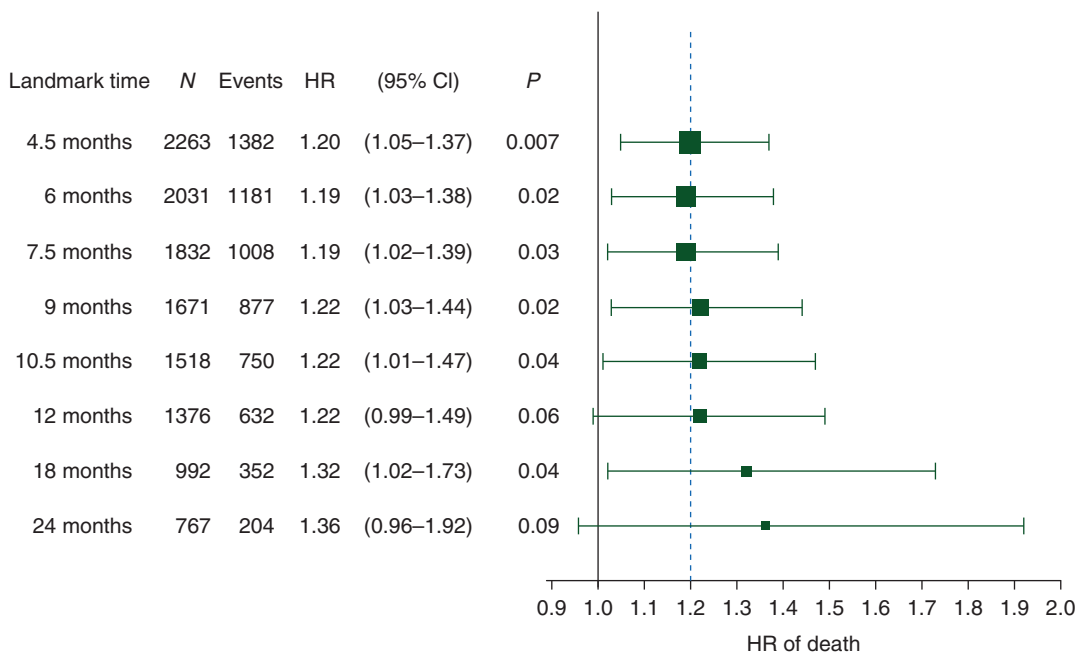


Figure 1. Association of financial toxicity with overall survival by variable landmark times (adjusted by gender, age, period, region, trial, baseline global QOL, global QOL response and baseline response to question 28). HR, hazard ratio. The size of the square is proportional to sample size.

significantly associated with an increased risk of death. Such findings, particularly the latter, were unexpected in the public Italian health system setting.

Due to the study design, it cannot be established to what extent baseline FB may be confounded by socio-economic

condition. Further, FT cannot be disentangled from disease progression, that is whether FT directly causes mortality or rather it is a consequence of cancer progression, that ultimately causes death. However, we can exclude that financial problems led to differential access to anticancer drugs, because in Italy no co-

payment for anticancer drugs is required. Therefore, our data extend the matter of financial difficulties beyond the cost of anti-neoplastic drugs. We may also speculate that it is unlikely that the effect of FT on survival be due to the increasing expenses close to the end of life [15], because results did not change with increasing the landmark time for survival analysis. Therefore, our data show that financial difficulties are a problem worthy of investigation even in public health frameworks.

Our study has some weaknesses. First, the population was selected for participation in a clinical trial, and may not be representative of the general cancer population in Italy and at risk of underrepresentation of patients with poor socio-economic status [16]. Second, as the present analysis was not planned when the clinical trials were performed, we did not collect information on demographics, socio-economic status and education level and cannot adjust for these possible confounders. Also, the location of the recruitment centre was used as a proxy for the place of origin of the patients and confusion could arise from the fact that some patients from Southern Italy migrate to Northern regions for cancer treatment (see the 2016 FAVO report at <http://www.favo.it/ottavo-rapporto.html>, accessed 30 August 2016). Third, we cannot speculate on factors predictive of financial burden or toxicity, because the patient population was not consecutive but selected according to availability of clinical trials and inclusion/exclusion criteria. Therefore, caution is required in interpreting the rate of patients with FB or FT as a measure of prevalence, because they might be biased. Finally, Q28 of the EORTC QLQ-C30 is a single-item question that does not allow distinction between financial difficulties generated by the cancer physical condition or the medical treatment itself.

However we believe that our study also has a number of strengths. First, it includes a very large series of patients, to our knowledge the largest ever based on prospective data collection and not originating from public registries, thus preventing typical selection bias of observational studies or cross-sectional surveys. Second, due to the trials' long term follow-up, we were able to prospectively measure the association of FB and FT with relevant clinical outcomes. Accordingly, we were able to distinguish between the prevalent FB and the incident FT, while these measures are usually confused in retrospective or cross-sectional studies. Third, the pragmatic approach of all the clinical trials pooled for this analysis, makes our findings reasonably generalizable to clinical practice, although validation is warranted. Fourth, sensitivity analyses confirm that our findings are robust and not substantially affected by any possible outlier trial. Further, all analyses were adjusted for global QOL (EORTC-C30 questions 29–30), either as baseline QOL or QOL response during the trial, that is recognized as an important prognostic factor in many settings (e.g. lung cancer [17]) and roughly stands as a proxy for many other potential confounding factors, both at baseline and during treatment. Fifth, as far as we know, this is the first report suggesting that financial problems might play a role in cancer patients' outcomes outside the US and in a public health system. However, we acknowledge that, even in a public third-payer framework where most services are cost free at the point of delivery, patients may pay for some services, like drugs for minor side effects which are not covered by the public payer, outpatient and inpatient services privately accessed, home health services. The latter might occur because of long waiting

lists, or because patients want to be treated by or have a second opinion by a health care professional who is not available through the public system. In such a context, patients might be more sensitive to the impact of financial constraints outside the health care system (e.g. working days lost by the patient or their relatives' travel and sojourn expenses if treated in a distant town, as also suggested by the Macmillan's research report 'Revealing the costs behind the illness' at <http://www.macmillan.org.uk>, accessed 30 August 2016).

More appropriate and context-driven measurement tools are needed. The COST score, a patient-reported-outcome instrument, has been recently proposed as a tool for measuring financial distress in US [18]. It is a questionnaire composed of 11 items, derived from an initial list of 147. This instrument has been applied to a cross-sectional pilot study including 100 insured multiple myeloma patients after at least 3 months of medical treatment [19]. However, it is not clear whether this questionnaire may work in different health systems.

For the future, a deeper understanding of the factors causing financial difficulty is required with the use of specific multidimensional instruments, tailored to the different socio-cultural contexts. With knowledge of causes and risk of financial difficulty, interventional strategies can be planned from optimization of health services to intensification of social support or stewardship activities in favour of cancer patients.

acknowledgments

The data pooled for this analysis derive from clinical trials that were done thanks to patients and their families, the participating Investigators who are listed in the previous publications of each trial, and thanks to cooperation of people working at the Clinical Trial Unit, NCI Naples: Giuliana Canzanella, Federika Crudele, Gianfranco De Feo, Antonia Del Giudice, Cristiana De Luca, Giovanni de Matteis, Manuela Florio, Marilena Martino, Teresa Ribocco, Fiorella Romano, Alfonso Savio, Lucia Sparavigna.

funding

None declared.

disclosure

The Authors have declared no conflicts of interest.

references

1. Mailankody S, Prasad V. Five years of cancer drug approvals: innovation, efficacy, and costs. *JAMA Oncol* 2015; 1: 539–540.
2. Saltz LB. Perspectives on cost and value in cancer care. *JAMA Oncol* 2016; 2: 19–21.
3. Ramsey S, Blough D, Kirchoff A et al. Washington State cancer patients found to be at greater risk for bankruptcy than people without a cancer diagnosis. *Health Aff* 2013; 32: 1143–1152.
4. Chino F, Peppercorn J, Taylor DH, Jr et al. Self-reported financial burden and satisfaction with care among patients with cancer. *Oncologist* 2014; 19: 414–420.

5. Zafar SY, Peppercorn JM, Schrag D et al. The financial toxicity of cancer treatment: a pilot study assessing out-of-pocket expenses and the insured cancer patient's experience. *Oncologist* 2013; 18: 381–390.
6. Delgado-Guay M, Ferrer J, Rieber AG et al. Financial distress and its associations with physical and emotional symptoms and quality of life among advanced cancer patients. *Oncologist* 2015; 20: 1092–1098.
7. Lathan CS, Cronin A, Tucker-Seeley R et al. Association of financial strain with symptom burden and quality of life for patients with lung or colorectal cancer. *J Clin Oncol* 2016; 34: 1732–1740.
8. Zafar SY, McNeil RB, Thomas CM et al. Population-based assessment of cancer survivors' financial burden and quality of life: a prospective cohort study. *J Oncol Pract* 2015; 11: 145–150.
9. Ramsey SD, Bansal A, Fedorenko CR et al. Financial insolvency as a risk factor for early mortality among patients with cancer. *J Clin Oncol* 2016; 34: 980–986.
10. Khera N. Reporting and grading financial toxicity. *J Clin Oncol* 2014; 32: 3337–3338.
11. de Souza JA, Yap B, Ratain MJ, Daugherty C. User beware: we need more science and less art when measuring financial toxicity in oncology. *J Clin Oncol* 2015; 33: 1414–1415.
12. Aaronson NK, Ahmedzai S, Bergman B et al. The European Organization for Research and Treatment of Cancer QLQ-C30: a quality-of-life instrument for use in international clinical trials in oncology. *J Natl Cancer Inst* 1993; 85: 365–376.
13. Fayers PM, Aaronson NK, Bjordal K et al., on behalf of the EORTC Quality of Life Group. The EORTC QLQ-C30 Scoring Manual (3rd Edition). Brussels: European Organisation for Research and Treatment of Cancer, 2001.
14. Osoba D, Rodrigues G, Myles J, Zee B, Pater J. Interpreting the significance of changes in health-related quality-of-life scores. *J Clin Oncol* 1998; 16: 139–144.
15. Seshamani M, Gray AM. A longitudinal study of the effects of age and time to death on hospital costs. *J Health Econ* 2004; 23: 217–235.
16. Sharrocks K, Spicer J, Camidge DR, Papa S. The impact of socioeconomic status on access to cancer clinical trials. *Br J Cancer* 2014; 111: 1684–1687.
17. Maione P, Perrone F, Gallo C et al. Pretreatment quality of life and functional status assessment significantly predict survival of elderly patients with advanced non-small-cell lung cancer receiving chemotherapy: a prognostic analysis of the multicenter Italian lung cancer in the elderly study. *J Clin Oncol* 2005; 23: 6865–6872.
18. de Souza JA, Yap BJ, Hlubocky FJ et al. The development of a financial toxicity patient-reported outcome in cancer: the COST measure. *Cancer* 2014; 120: 3245–3253.
19. Scott F, Huntington BMW, Dan T et al. Financial toxicity in insured patients with multiple myeloma: a cross-sectional pilot study. *Lancet Haematol* 2015; 2: e408–e416.