Under-reporting of harm in clinical trials

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Appropriate safety evaluations of anticancer drugs are crucial to assess their benefit–risk ratio. Substantial evidence shows that clinicians under-report harm in clinical trials, and at least three factors contribute to this problem: assessment of harm by clinicians might not represent the experience of patients; harm might be detected within trials, but is not reported appropriately by investigators or reporting is influenced by sponsors; and short-term follow-up might not detect long-term and potentially serious toxicities. Additionally, because of the selection of patients with good functional status in clinical trials, study results might not apply to patients treated in everyday clinical practice. New approaches for the conduct, oversight, and reporting of clinical trials should include patient-reported assessment of side-effects. Effective pharmacovigilance programmes and large-scale observational studies are needed to improve understanding of the tolerability of anticancer drugs in a real world setting.

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Introduction

The aim of phase 3 randomised controlled trials in oncology is to identify new therapies with a favourable benefit–risk ratio. However, existing approaches for assessment of outcomes (except for overall survival) are usually not patient centred and might not be optimal; specifically, information about side-effects and safety is almost exclusively reported by the trial investigators.[1] Drug labels contain information about the safety of new drugs, which is based mainly on laboratory evaluations or clinicians' impression of patients' symptoms. However, 40–50% of adverse events reported on US Food and Drug Administration (FDA) labels for drugs for treatment of breast cancer and various non-malignant disorders are symptoms, which can only be assessed accurately by patient self-reporting.[1] Furthermore, clinicians usually base their assessment of the benefit–risk ratio of a drug on reports of clinical trial results, which highlights the importance of a balanced presentation of study results by the investigators without influence of the sponsors (often pharmaceutical companies). Once approved, new anticancer drugs can be prescribed to patients with poorer overall health than those who participated in the clinical trials. Therefore, a benefit–risk ratio of new drugs might be less favourable in a real-world setting than in clinical trials. We review the problem of underdetection and under-reporting of harms of new anticancer drugs, and discuss possible solutions to mitigate it.

Reporting of harm

Discrepancy

Reporting of adverse events in clinical trials is one of the key components of clinical cancer research to ensure patients' safety and clinicians' understanding of the toxicity profiles of new anticancer drugs. The Common Terminology Criteria for Adverse Events (CTCAE), developed by the US National Cancer Institute (NCI) is a system of nomenclature to classify adverse events and their associated severity in clinical trials of anticancer drugs.[2] This system contains three categories of adverse events: laboratory-based adverse events, observable or measurable adverse events, and symptomatic adverse events reported by patients. The CTCAE has been updated continuously via a consensus-based process and has been adopted widely.[3] The CTCAE was introduced in 1982 when most anticancer agents were given intermittently and had transient toxic effects. By contrast, continuous use of modern targeted agents can cause recurrent or chronic symptomatic toxicities. Low-grade chronic toxicities might substantially affect patients' lives, and their effects might not be optimally captured by the existing CTCAE system.[4] For example, grade 3 diarrhoea lasting for 1–2 days might be less bothersome for a patient than grade 2 diarrhoea lasting for several weeks.

Agreement between different clinicians in reporting of symptomatic adverse events via the CTCAE is suboptimal (table 1).[5] Whether the absence of reliability in reporting of adverse events among clinicians is attributable to the CTCAE, or whether it is an inherent limitation of reporting of adverse events by clinicians, is unknown. Moreover, because the process of reporting symptomatic adverse events is not standardised, interpretations of a patient's symptoms by clinicians and research assistants might be suboptimal.[13] Increasing evidence shows that, compared with patients, clinicians (physicians and nurses) under-detect and under-report symptomatic adverse events of anticancer drugs, both in everyday clinical practice[1,6,7,9–11] and clinical trials[6,8,12] (table 1). Several reasons might explain this effect: insufficient time during patients' visits to fully discuss symptoms, under-reporting of symptoms by patients because of their desire to remain on therapy, and downgrading of symptoms by clinicians to justify continuation of treatment.[5] Some symptoms experienced by patients might be attributed to underlying disorders (ie, non-treatment related) rather than to the investigational product (ie, treatment related), and might therefore not be reported properly by investigators. Furthermore, ascertainment of treatment-related and non-treatment-related adverse events in clinical trials might be prone to bias because the toxicity profile of standard therapy given to the control group is likely to be more widely understood than that of the experimental therapy.

	Aim of study	Sample and study design	Results and interpretation
Clinician *vs* clinician symptom reporting			
Atkinson and colleagues (2012)[5]	To assess the reliability of adverse events reporting by clinicians for the same patient and same visit	393 patients with cancer treated in a single centre (90 [23%] of whom were in clinical trials); a retrospective reliability study in which each patient was seen and assessed by two clinicians (physician or nurse), who independently rated seven CTCAE symptoms	Agreement between clinicians was moderate: interclass correlation coefficients were 0·46–0·69 for symptoms and were stable over time; different symptom ratings* that would affect treatment decisions occurred in 18% of patients with constipation, 8% of patients with nausea, and 15% of patients with vomiting
Clinician *vs* patient symptom reporting			
Di Maio and colleagues (2015)[6]	To compare reporting of adverse events by patients and physicians	1090 patients from three RCTs (breast cancer and NSCLC, including elderly patients); six symptomatic toxicities were prospectively assessed by investigators with the CTCAE at the first three visits; patients completed EORTC QoL questionnaires at the end of each cycle	Agreement between patients and physicians was low for all toxicities. For patients who reported toxicity of any severity, under-reporting by physicians was 41–74%; with examination of only patients who reported severe toxicity, under-reporting by physicians was 13–50%
Novello and colleagues (2014)[7]	To compare reporting of adverse events by patients and physicians	116 patients with advanced NSCLC treated with targeted drugs in everyday clinical practice; the survey required monthly compilation of physicians' and patients' questionnaires, basing adverse event assessment on CTCAE; physicians and patients assessed toxicity and QoL at three consecutive visits	Results show underestimation of toxicities by clinicians compared with patients; at every visit, a significant difference in perception of targeted therapy-related toxicities of any type and grade was described (p=0·0001 in all cases); the difference between physician and patient reporting was greater for adverse events more strongly associated with daily life and QoL
Quinten and colleagues (2011)[8]	To assess the extent to which patient and clinician symptom scoring and their agreement could contribute to the prediction of overall survival in patients with cancer	2279 patients with cancer from 14 closed EORTC clinical trials; investigators analysed baseline data for six cancer symptoms, which were assessed by both patients and clinicians; the extent of agreement and potential for clinician-reported or patient-reported symptom scores to improve the accuracy of Cox models to predict overall survival were assessed	Patient-reported scores for some symptoms, especially fatigue, differed from clinician-reported scores; Cox models of overall survival that considered both patient and clinician scores had more predictive accuracy than models that considered clinician's scores alone for each of four symptoms
Basch (2010)[1]	To assess cumulative incidence of adverse events over time as reported by patients *vs* clinicians at successive office visits	467 patients with cancer; patient-reported symptoms collected at 4034 clinic visits; patients and clinicians reported adverse events according to the CTCAE; overall health status assessed by EuroQoL EQ-5D	Patients reported moderate-severity symptoms earlier and more frequently than did clinicians; patients' reports were more highly concordant with overall health status than were clinicians' reports
Basch and colleagues (2009)[9]	To compare how patients' *vs* clinicians' reports relate to sentinel clinical events	163 patients with lung cancer treated with chemotherapy; patients independently reported six CTCAE symptoms and Karnofsky Performance Status longitudinally at sequential office visits	Patients generally reported symptoms earlier and more frequently than did clinicians; significant associations with death and emergency room admissions were recorded for clinician reports of fatigue (p<0·001), nausea (p=0·01), constipation (p=0·038), and Karnofsky Performance Status (p<0·001), but not for patient reports of these items; higher concordance with EuroQoL EQ-5D questionnaire and global question scores was observed for patient-reported symptoms than for clinician-reported symptoms
Pakhomov and colleagues (2008)[10]	To assess agreement between patient-reported symptoms and documentation of these symptoms by physicians in electronic medical records	1119 patients: chest pain (N=373), dyspnoea (N=391), cough (N=337), multiple symptoms (N=18); three symptoms reported by patients were compared with those identified with language processing of the text of clinical notes from care providers	There was a positive agreement for 74 patients and a negative agreement for 78 patients with chest pain between patient's report and clinical note; among 391 patients with dyspnoea, there was a positive agreement for 70 patients and a negative agreement for 76 patients; among 337 patients with cough, there was a positive agreement for 63 patients and a negative agreement for 75 patients; κ statistics were 0·50 for chest pain, 0·46 for dyspnoea, and 0·38 for cough
Basch and colleagues (2006)[11]	To compare reporting of symptom severity by patients and clinicians	400 patients with cancer at one institution; a questionnaire with 11 common CTCAE symptoms (an adapted version of the CTCAE) was given to consecutive outpatients and their clinicians (physicians and nurses); clinicians were aware that comparisons would be made	For most symptoms, agreement between patients and clinicians was high, and most discrepancies were within a grade difference of one point; agreement was lower for subjective symptoms; differences in symptom reporting rarely would have changed treatment decisions or dosing, and patients assigned greater severity to symptoms than did clinicians
Fromme and colleagues (2004)[12]	To compare patient reporting of eight symptoms using the EORTC QLQ-C30 questionnaire with physicians' reporting of the same symptoms in the study's adverse event log	37 men with mCRPC enrolled in a phase 2 study; a patient-reported symptom was defined as an increase in a symptom score by at least 10 points (on a 0–100 scale), sustained for at least 4 weeks; a physician-reported symptom was judged to be present if it was documented in the adverse event log	49 (new or worsened) symptoms were detected by both physician and patient, 48 symptoms were detected by the physician alone, and 55 symptoms were detected by the patient alone; corrected Cohen's κ was 0·15, indicating only slight agreement; overall physician sensitivity was 47% and specificity was 68%

CTCAE=Common Terminology Criteria for Adverse Events. RCT=randomised controlled trial. NSCLC=non-small-cell lung cancer. EORTC=European Organisation for Research and Treatment of Cancer. QoL=quality of life. mCRPC=metastatic castrate-resistant prostate cancer. *The frequency of disagreement of two or more grade points between raters on the CTCAE, which might affect treatment decisions.

Table 1: **Reporting of harm by clinicians and patients**

Clinicians might not record symptoms reported by patients, and might also downgrade the severity of patients' symptoms, which can lead to new, otherwise preventable, adverse events.[10,14] For example, inappropriate management of nausea might lead to serious fluid and electrolyte imbalances, which can result in kidney failure or arrhythmia. Furthermore, patient reporting seems to detect symptoms attributable to potentially serious adverse events earlier than does clinician reporting.[1,15] Patients' and clinicians'