Systematic Review of adverse events reporting in clinical trials leading to approval of targeted therapy and immunotherapy

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Introduction

The detailed knowledge of the risks associated with the administration of anti-cancer treatments is crucial for multiple stakeholders, including regulatory authorities, clinical researchers, physicians and - of course – patients[1]. About twenty years ago, the Outcomes Working Group of the American Society of Clinical Oncology's Health Research Committee defined toxicity as a vitally important outcome, among those to be used for technology assessment and development of cancer treatment guidelines[2]. In fact, a complete and accurate description of the frequency, the duration and the severity of adverse events (AEs) associated with the administration of anti-cancer agents is crucial for an informed evaluation of their risk / benefit profile. According to a modern concept of evidence-based clinical practice, an exhaustive communication between patients and physicians about benefits and risks associated with treatments ensures that patients' preferences are adequately taken into account in decision-making, and is crucial for an optimal care[3].

In the case of newly approved treatment, information about adverse events is substantially based on the reports of pivotal clinical trials. A suboptimal reporting and description of toxicity available in the publications could substantially affect the absolute estimates of its burden, which is highly relevant information for the applicability of trial results in clinical practice, particularly for new drugs.

In recent years, reporting of AEs by investigators, coded and graded through the Common Terminology Criteria for Adverse Events (CTCAE), has been the most commonly used method of quantifying treatment harm to patients[4]. Without doubt, the wide adoption of CTCAE has represented a major step in terms of standardization and harmonization of toxicity reporting[5]. However, several aspects need to be substantially improved.

First, it is well known that many subjective toxicities are at risk of under-reporting when the report is exclusively based on physicians' records[1,6]. To reduce this under-reporting, the scientific interest in the integration of patient-reported outcomes into description of AEs is growing[1]. An integrated approach, where the patients directly report symptomatic toxicity information, could really improve the efficiency of reporting[7].

Second, differently from traditional chemotherapy, that is often administered for a limited number of cycles, many of the drugs newly approved in oncology (including targeted therapies and immunotherapy) are administered until disease progression, often for many months, sometimes also for years. With these drugs, the usual reporting – based on the description of the worst grade of toxicity experienced by each patient – is not appropriate to fully capture the tolerability profile[8]. Thereby, a complete description of toxicity should adequately take into account the time of occurrence of toxicity, its duration and its modification (improvement or worsening) over time: even low-grade toxic effects, especially if long-lasting, can have a relevant impact on quality of life[9].
Third, independently of the quality of data collection, the report of toxicity can be suboptimal in terms of completeness of data presented in the publication[10,11]. Data collection on AEs is generally limited at the duration of the trial. Partially due to length limitations imposed by most scientific journals, the information included in the abstract, in the main text and in the tables is often incomplete. Moreover, the modality of presentation of toxicity data is highly heterogeneous among different publications, even within the same journal.

Aim of this systematic review is to describe the quality of the reporting of AEs in the publications of pivotal clinical trials testing new drugs (molecularly targeted agents and immunotherapy) in solid tumors.

Material and methods

Search strategy and selection criteria
We identified all the targeted therapies and immunotherapies approved by FDA for solid malignancies in adult patients from January 2000 to October 2015. The trials which led to this indication were retrieved from the FDA website (http://www.accessdata.fda.gov/scripts/cder/drugsatfda).

We performed a cross-search through MEDLINE via PubMed (http://www.pubmed.gov) to identify all publications of the trials.

In case a certain treatment was approved for more than one type of cancer, then all the trials performed in each different disease were considered.

A 24-point quality score (QS) was adapted from the extension of Consolidated Standards of Reporting Trials (CONSORT) statements for reporting harms-related data[12]. The QS was divided according to the sections reported in each trial: Title/Abstract/Introduction (3 items), Methods (6 items), Results (13 items) and Discussion (2 items). Compared with the traditional reporting of AEs associated with chemotherapy, immuno-related adverse events, as previously recognized[13], and targeted-treatment toxicities have some peculiar characteristics, related to time of occurrence and duration, which were better captured by the adapted QS. Specifically, the elements included in this analysis and not previously evaluated in other CONSORT adaptation[10,12-13] were: the report of duration of AEs, the record of all AEs or only above a certain frequency or rate threshold, the description of AEs leading to treatment withdrawal, the evaluation of recurrent and late toxicities (considered as new toxicities that occurred after treatment completion, as well as toxicities that developed during therapy and continued after therapy was completed)[14]. All the 24 items had a score of 0 point for incomplete, 1 point for complete reporting or 0.5 point for partial reporting, in case at least one AE was specified according to the requested quality characteristic or if the item was partially satisfied.

Each paper was scored by 2 independent assessors and the discrepancies was solved by a third evaluator. The following data were also considered for each paper: year of publication, impact factor of the journal, type of disease, setting of treatment (curative or palliative), therapy employed as single agent or in association with chemotherapy, radiation or other targeted agent, type of treatment (targeted agent or immunotherapy), dose of the drug (fixed or adjusted on body weight or body-surface area), type of drug (small molecule or antibody), mode of administration (continuous or intermittent), route of administration (orally or intravenous), total number of patients treated, rate of elderly patients (more than 65 years old), control arm (placebo or active treatment), sources of funding (industry or not), results of primary outcome of the trial (positive or negative), number of participating centres, phase of the trial.

Statistical part
We summarized the completeness of adverse event calculating the QS for each trial, by summing the score for each item partially (0.5 points) or completely (1 point) reported.

We performed univariate and multivariate linear regression to investigate the association between the main analyzed factors and the completeness of adverse events reporting. The characteristics included in the regression were: the impact factor of the publishing journal based on what reported the Journal Citation Reports of year 2015[15] (<20 or $\geq$20); year of publication ($\leq$ 2010 or > 2010); treatment combination (if the investigated drug was studied alone or if associated with chemotherapy, hormonal therapy, other targeted agents, radiotherapy or other immunomodulatory therapies); source of funding (industry versus non-industry); result of primary outcome (positive versus negative) and setting of the cure (curative, palliative or both). Covariates with a $P < 0.15$ in the univariate model were included in the one-step multivariate model. Furthermore, we used the likelihood ratio test, which compares the goodness of fit

between models, to identify the variables to be included in the multivariable model. Covariates were considered statistically associated with the QS if the p value is lower than 0.05.

Results

We identified 81 trials that globally involved 45,084 patients. Characteristics of the trials are reported in Table 1 and the corresponding references are reported in the supplementary material. These trials were mainly conducted in a palliative setting (95.1%), recruiting patients with unresectable or metastatic disease. Only three trials (3.7%) were conducted in an adjuvant setting and one (1.2%) included patients with both curable and advanced disease. Eligible trials were principally performed in patients affected by colorectal (19.8%), lung (13.6%), breast cancer (12.4%), and melanoma (12.4%).

The identified trials analyzed either a single-agent drug or a combination of targeted therapies or immunotherapies with other cancer treatments (that is, chemotherapy, radiotherapy, other targeted therapies, or other drugs or radiation). In detail, more than half of the trials concerned single-agent therapies (50.6%), whereas the remaining included combination therapies, mainly with chemotherapy (32.1%). Details (drugs considered and references) of all the analyzed trials are reported in the supplementary material.

The trials included in the analysis were mainly funded by industries (96.3%) and, as far as the primary endpoint is concerned, the vast majority had a positive outcome (97.5%).

The vast majority of the considered trials were phase II (11.2%) and III (86.2%) trials. There was one phase IV study, while the only phase I trial analyzed was the one that led to approval of ceritinib in metastatic ALK-mutant non-small cell lung cancer. In this study, the maximum tolerated dose (MTD) was not reached.

The number of patients above 65 years old was reported in 45 studies (55.6%). Considering only the trials that reported this information, only 10% of these had at least half of the patients enrolled with an age above 65 years, while in 50% elderly patients represented less than 36% of the total number of included patients.

Main results of the QS are reported in figure 1 and 2 and in supplementary figure 1. The concordance between evaluators in assessing each item was very high (rate of discordance less than 5%).

The main critical points were the report of recurrent and late toxicities, respectively lacking in 98% and 95% of the studies, the lack of information about the duration of the adverse events (94% of the studies), the lack of description of the time of occurrence (86% of the trials), and the lack of report of all the events, instead of only those occurring above a fixed threshold of patients (75% of the trials).

Other relevant inadequacies were found in the report of the statistical methods for presenting AEs (63%), in the description of the toxicities that caused therapy withdrawal (57%), and in the description of the follow up interval assessments (51%).

Only 38% of the entire pool of the considered articles reported the number of patients who required a dose adjustment (whenever this was permitted) due to AEs.

Table 2 describes the results of univariate and multivariate analysis of factors associated with the completeness of adverse events reporting.

At the univariate analysis, the significant parameters were the journal impact factor equal or higher than 20 ($p = 0.005$), the year of publication after 2010 ($p = 0.0002$), the positive result of the primary outcome ($p = 0.013$), fixed dose of the considered drug ($p= 0.0024$) and use of monotherapy ($p=0.0009$).

At the multivariate analysis only a few parameters were found statistically significant, that is the year of publication after 2010 ($p = 0.006$), impact factor ($p=0.046$) and the result of the primary outcome ($p = 0.0361$).

Number of participating centers did not correlate with the QS, both if considered as continuous variable and when considering as cut-off the median number (88).

Discussion

This systematic review showed suboptimal reporting of AEs in the papers describing the trials leading to approval of targeted treatments and immunotherapies, as insufficient data was shown in most of the trials regarding the reporting of duration of AEs, recurrent and late toxicities, the lack of description of time of occurrence and the lack of report of all adverse events. We strongly believe that a suboptimal report of adverse events in publications of trials with anticancer drugs can impair a proper evaluation of the benefit-risk profile of treatments used in clinical practice. This concept was already emphasized in 2004, when the CONSORT published minimum standards for improved description of harms, because the authors were convinced that a better reporting can help readers critically appraise and interpret trial results[12]. More recently, pharmaceutical industry and journal editors proposed recommendations to communicate drug adverse events in a more informative and clinically meaningful manner, in order to avoid incomplete or erroneous judgments on the perceived benefit to harm profile of a treatment[16].

One of the most relevant weaknesses we assessed was the limited attention to duration of toxicities. Duration could be defined as "the third axis" of toxicity assessment (the other 2 being frequency and severity of a symptom). In detail, description of the time of occurrence of AEs was missing in 86% of the trials, duration of grade 3-4 AEs was not reported in 94% and more than half of the publications did not describe the follow up interval assessments. We believe that the simple report of the most severe grade experienced by each patient maybe could be sufficient as a partial, gross measure of the "clinical risk" associated with the AE, but it is not sufficient to quantify the potential impact on the health-related quality of life. For instance, in case of toxicities like nausea, or diarrhea, or fatigue, a grade 1-2 adverse event can produce a very different impact on patient's quality of life and functional status according to its duration. This applies to many of new anticancer drugs, that differently from chemotherapy are administered until disease progression, often with a continuous daily assumption. Recently, the Toxicity over Time (ToxT) approach was proposed by Thanarajasingam and colleagues[17], with the aim of developing a more comprehensive depiction of toxic effects than the methods currently used in most trials. Interestingly, the ToxT approach combines graphs and tables of toxicity with statistical methods in order to describe the changes in AEs across all cycles of treatment, the time-to-event analyses of first and worst grade toxicity, and the area under the curve (AUC) analyses summarising AE profiles over the entire course of a study.

Another major limitation in the description of toxicities was found in the report of recurrent and late toxicities. One possible explanation of this fact is that many new drugs undergo a fast-track approval process due to their high activity and to the fact that they tackle an unmet need. In this way, fast-track approval may lead to an underestimation of late toxicities

As matter of fact, with new immunotherapeutic drugs (mainly with checkpoint inhibitors) potentially rare but severe AEs may occur late after drug initiation, even months after treatment end. This emphasizes the need of precise and timely report of toxicities after drug approval, also implementing phase IV post-marketing trials, designed to obtain a more complete description of the toxicity profile of these new drugs. A call to change has been recently suggested in toxicity reporting from phase I trials, particularly with molecularly targeted agents. In fact, AEs may often happen after the first cycles of therapy (so after the end of the protocol-defined dose limiting toxicities period, DLT), and AEs may score as DLT even if of grade <3. The Authors urge to take into account lower grade and delayed toxicities into the dose-recommendation process [18].

Frequently (that is, 75% of the publications examined in the review), papers lack to report all the AEs occurred in the trial, analysing only those occurring above a fixed threshold of patients. The incompleteness in the description of toxicities in many publications has been already described. In a review of the assessment and reporting of toxicity in phase II trials dedicated to breast cancer patients, Perrone and colleagues[19] noted that almost none of them contained a statement that all the observed toxicities had been reported, implying that, when a toxicity was not reported in the publication, the reader could not state if such AE was not observed or not reported due to its low frequency. In the same analysis, the

reporting of degrees of toxicity was incomplete in approximately one third of the studies, being limited to the description of severe toxicities.

We understand that the decision of presenting an incomplete description of the observed toxicities is often related to editorial needs, due to limitations in the length of text and in the dimensions of tables. However, considering that most journals allow the attachment of supplementary material to the publication, it should be mandatory to include, at least in the appendix, a complete report of all experienced AEs.

Other relevant inadequacies were found in the report of the statistical methods for presenting AEs (63%) and the description of the toxicities that caused therapy withdrawal (57%). In our opinion, this latter aspect is crucial when evaluating the impact of a given treatment on a single-case basis in the "real-life population", especially in the context of advanced disease when the common rule of "first, do no harm" is essential.

It is also interesting to notice that only the 38% of the considered articles reported the number of patients who required a dose adjustment (whenever this was permitted) due to AEs. The rate of dose adjustment could add a new layer in the interpretation of the risk/benefit ratio of a treatment, giving the physician an instrument to further tailor clinical decisions. For example, if treatment efficacy is maintained despite a high rate of dose reduction, one could pragmatically argue, that even when dose reduction is necessary there is still a good chance to achieve the therapeutic goal. By contrast, not knowing how many patients required a reduction of treatment dosage due to AEs makes impossible to ascertain the relative weight of reduced dosages when interpreting the whole results of a study. Moreover, as toxicities leading to dose reductions, when reported, are often unspecified (with mild laboratory abnormalities unperceived by the patients mixed with clinically relevant AEs), the translation of these data into a clinical decision making process could be hard. It should be also added that no trial reported the reversibility of AEs after dose reduction. In this context, a thorough description of toxicities leading to dose adjustments would add precious information, as well as the information about the impact of dose reduction on the same AEs.
We decided to study targeted agents and immunotherapy drugs approved by FDA due to the peculiar characteristics of these treatments and their related toxicities in comparison with the ones induced by chemotherapy. In this regard, we compared our results with the ones reported by Sivendran and colleagues, who considered more than 96,000 patients undergoing anticancer treatment (47% of the analysed articles was conducted with chemotherapy alone)[10]. Data from this study are consistent with our work in underlining the lack of reporting all AEs (and not only those occurring at a certain frequency) and in the lack of specifying recurrent events. However, in our analysis of the completeness of AE reporting, we highlighted the aspects of duration of toxicities which was less considered with cytotoxic agents.

We acknowledge that the published reports of studies represent only a summary of a dataset that may not necessarily represent the full data set submitted to licensing authorities for purposes of drug approval and registration. However, we consider that the published papers represent one of the main source of information for the clinicians in their practice, the basis for clinical choices and for an open discussion with the patients regarding the risk/benefit ratio of starting a new treatment. It was encouraging that, at multivariate analysis, a more recent year of publication resulted associated with a better completeness of adverse events reporting. However, higher impact factor of the journal was another factor independently associated with better reporting, emphasizing that, beyond the accuracy and completeness of data collection, the quality of authors' instructions and of editorial rules, along with the severity of peer reviewing process, can substantially improve the report.

Improving AEs caption and description, also with the employment of new methods, such as the newly implemented Patient-Reported Outcome (PRO) CTCAEs or the suggested Toxicity Over Time (ToxT) should be a priority in ongoing trials as well as post-marketing safety analysis. The need of improving the description of toxicity, particularly in terms of duration and recurrence, is particularly crucial if we consider that most of the newly approved anticancer agents (like tyrosine kinase inhibitors or immune checkpoint

inhibitors) are administered in a continuous schedule, and are associated with peculiar toxicities, with a clear impact on patients' quality of life.

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Conflict of interest: BoP reports personal fees from Astra Zeneca, Roche, Kyowa Kirin, Tesaro**,** Helsinn, Merck-Serono, outside the submitted work. LDL reports personal fees from Eisai, outside the submitted work. DMM reports personal fees from Bayer, Merck Sharp & Dohme, Eli Lilly, Astra Zeneca, and grants from Amgen, outside the submitted work. AA reports grants from Amgen, MSD, and Tesaro, outside the submitted work.

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Table 1

Characteristics of articles included in the analysis

Number of eligible trials (N, %)	81 (100)
Number of included patients	45,084
Setting	
Palliative	77 (95.1)
Palliative and curative	1 (1.2)
Curative	3 (3.7)
Primary site	
Colon and rectum	16 (19.8)
Lung	11 (13.6)
Breast	10 (12.4)
Melanoma	10 (12.4)
Kidney	8 (9.9)
Pancreas	4 (4.9)
Soft tissue sarcoma	4 (4.9)
Thyroid	4 (4.9)
Gynaecologic tumors	3 (3.7)
Stomach	2 (2.5)
Basal cell skin cancer	2 (2.5)
Giant cell tumour of the bone	2 (2.5)
Glioblastoma	2 (2.5)
Head and Neck	2 (2.5)
Liver	1 (1.2)
Sources of funding	
Industry	78 (96.3)
No industry	3 (3.7)
Results of primary outcome	
Positive	79 (97.5)
Negative	2 (2.5)
Phase of the trial	
1 and 2	10 (12)
3 and 4	71 (88)
Type of agent	
Targeted agent	74 (91.3)
Immunotherapy	7 (8.7)
Small molecules or antibodies	
Small molecules	40 (49.4)
Antibodies	41 (50.6)
Administration schedule	
Continuous	31 (38.3)
Intermittent	50 (71.7)
Route of administration	
Oral	38 (46.9)
Intravenous	43 (53.1)
Dose of the drug	
Fixed	42 (51.8)
Adjusted on BW or BSA	39 (48.2)
Monotherapy or combination	

Monotherapy	42 (51.8)
Combination	39 (48.2)
Number of participating centers (median, range)	88 (1 – 224)
Number of enrolled patients (median, range)	424 (37 – 3,351)
Year of publication of the manuscript	
Before 2010 (2010 included)	36 (44.4)
After 2010	45 (55.6)
Impact factor of the journal of publication	
< 20	21 (26)
≥ 20	60 (74)

Abbreviations: *BW: body weight; BSA: body surface area*

Table 2
Univariate and multivariate analysis

Study characteristics	Quality score		Univariate		Multivariate	
	Median	*Range*	*Coefficient*	*p values*	*Coefficient*	*p values*
Impact factor						
< 20	11.5	8-17	Ref			
≥ 20	14	5.5-18	1.83	**0.005**	1.16	0.046
Year of publication						
≤ 2010	12.5	5.5-17.5	Ref			
> 2010	14	10-18	2.07	**0.000**	1.47	**0.006**
Source of funding						
Industry	13.5	5.5-18	Ref		NA	
No industry	13	8-14	-1.83	0.232	NA	
Results of primary outcome						
Positive	13.5	5.5-18	Ref			
Negative	9	8-10	-4.54	**0.013**	-3.42	**0.036**
Setting						
Curative	13.5	8-18	Ref			
Curative and palliative	16	5.5-16	-0.92	0.548	NA	
Palliative	17	17	3.6	0.171	NA	
Phase of the trial						
3 and 4	13.5	5.5-18	Ref			
1 and 2	12.75	8-17.5	-0.43	0.626	NA	
Fixed dose or according to BW/BSA						
Fixed dose	14	10-17	Ref			
BW/BSA	13	5.5-18	-1.71	**0.002**	-0.69	0.249
Monotherapy or combination						
Monotherapy	14	10-18	Ref			
Combination	13	5.5-16.5	-1.86	**0.000**	-0.73	0.23
Type of drug						
Targeted agent	13.5	5.5-17.5	Ref			
Immunotherapy	16	11.5-18	-1.72	0.092	NA	

Abbreviations: *BW: body weight; BSA: body surface area*

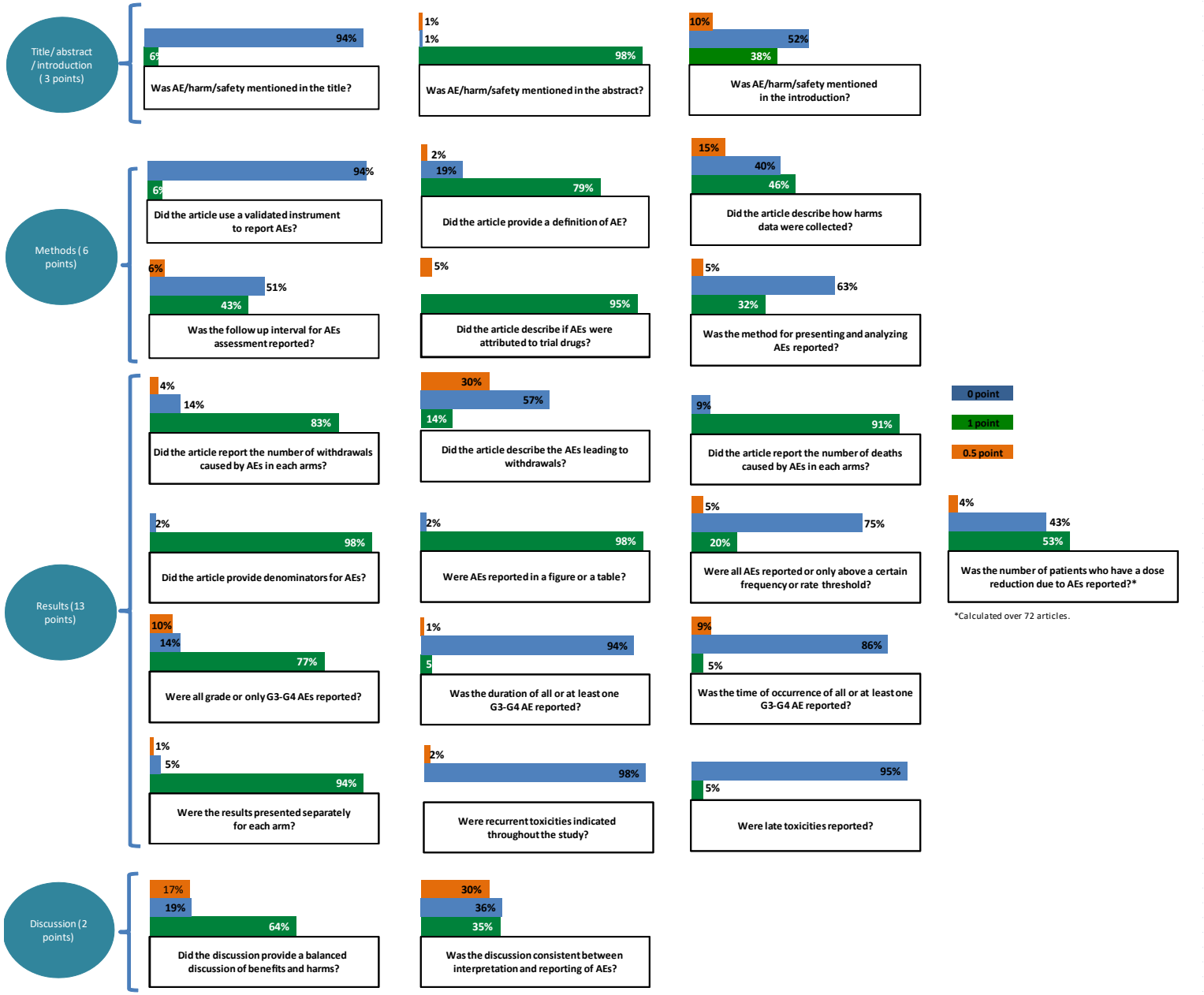

Figure 1. Components of the 24-point quality score and the scoring of each item from the 81 clinical trials

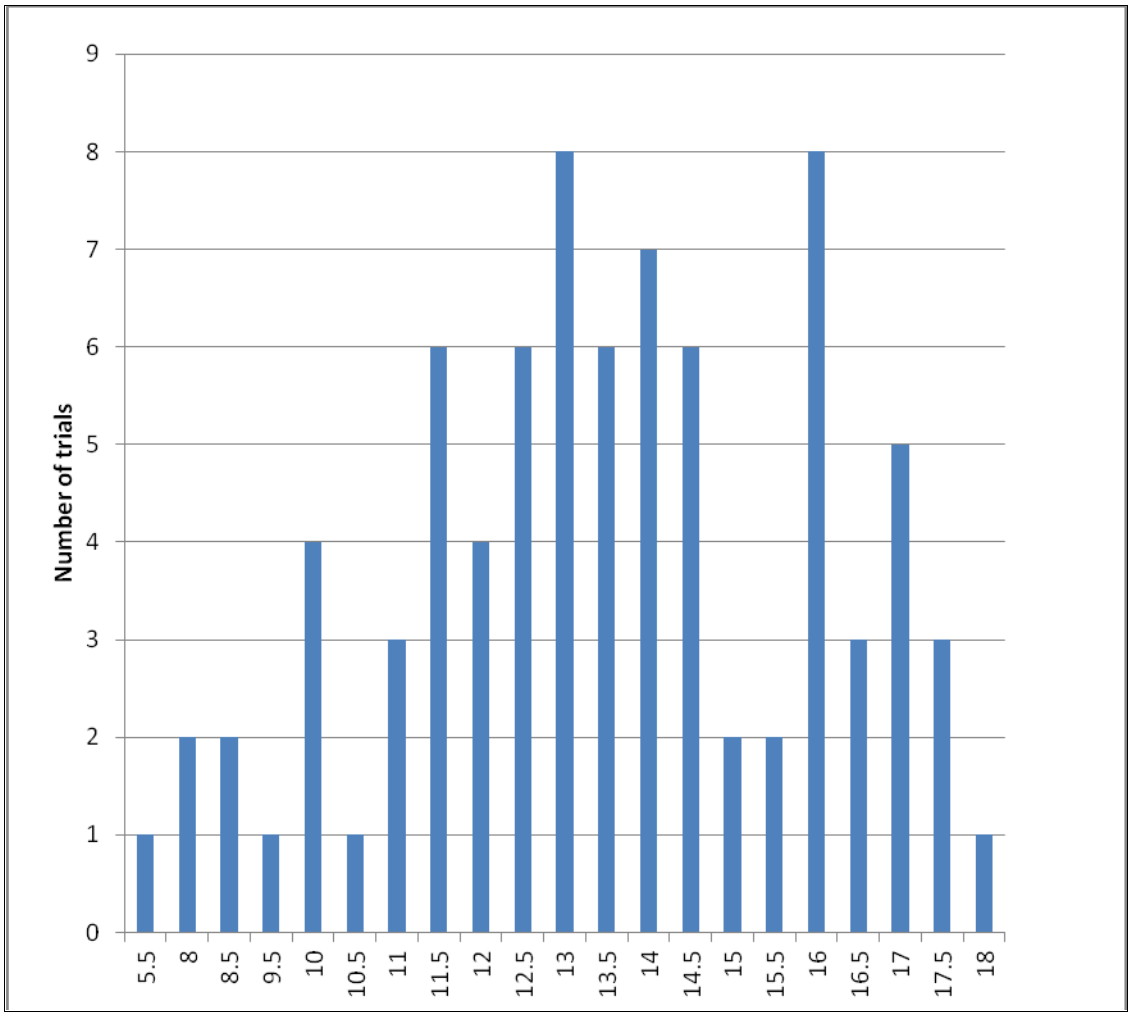

Figure 2. Distribution of the Adverse Events Quality Score

Fig S1a and S1b. Quality Score (QS) of each item according to the type of drug considered

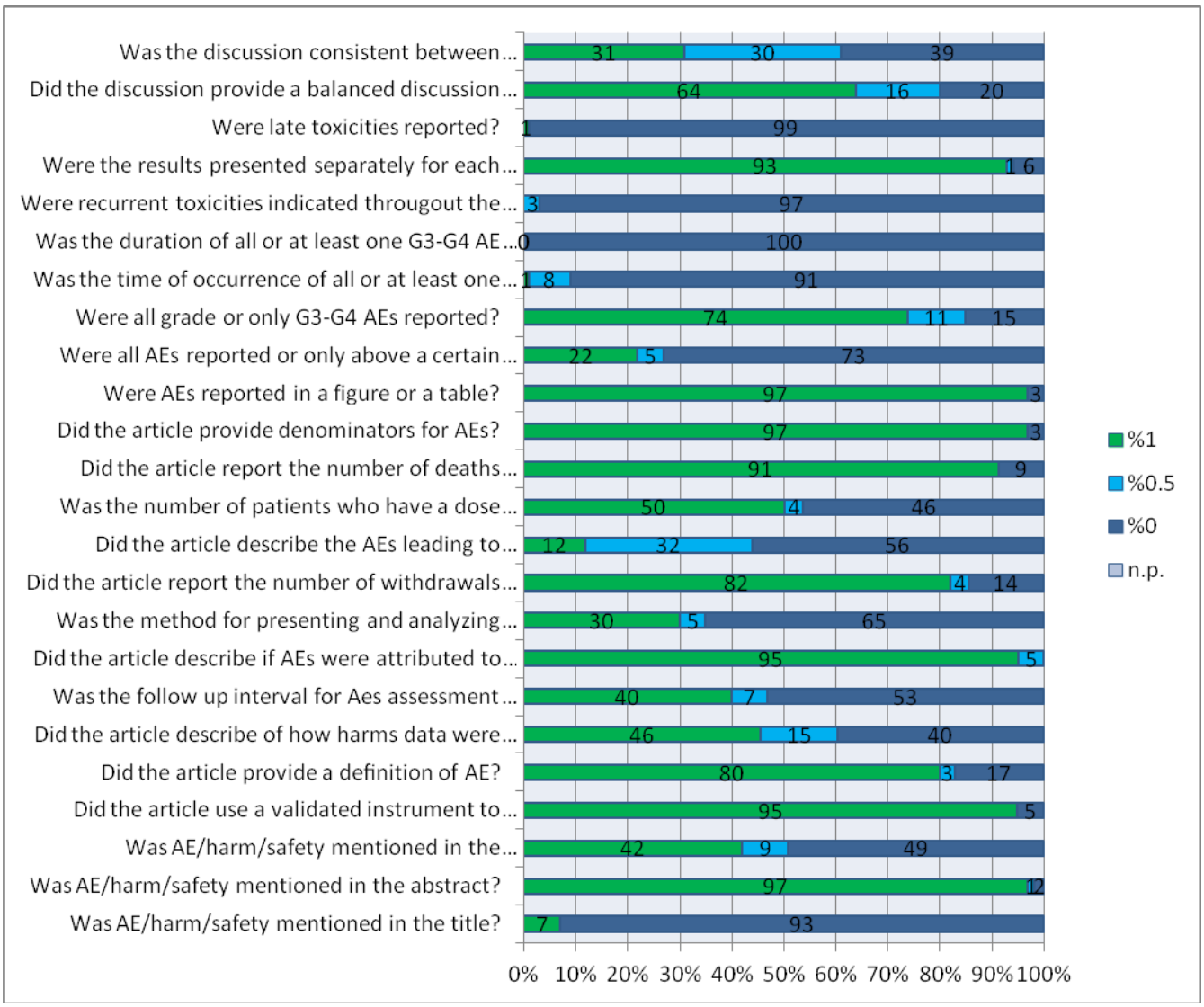

Fig S1a. QS of trials with targeted agents

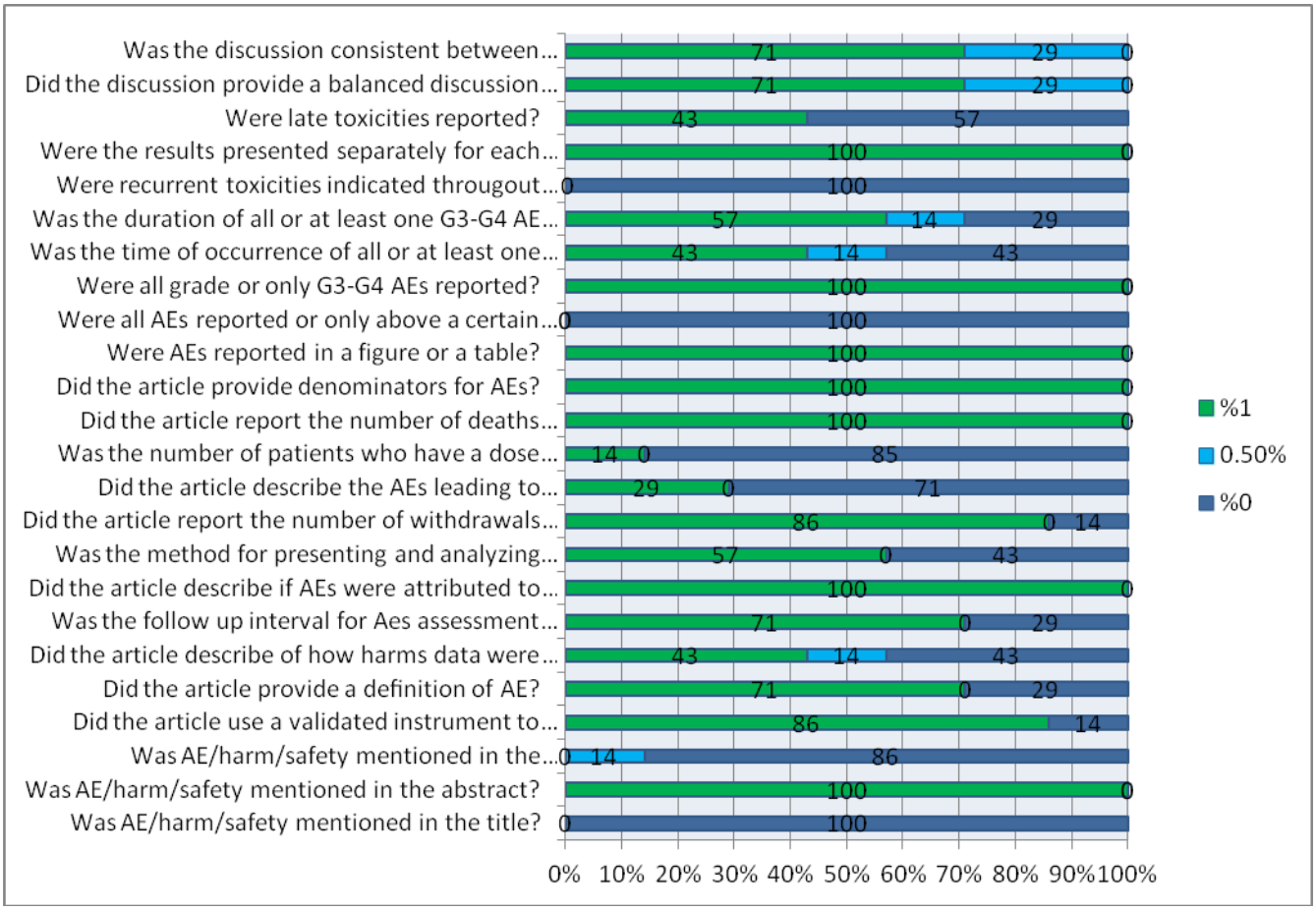

Fig S1b. QS of trials with immunotherapy

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