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A systematic review of immune-related adverse event reporting in clinical trials of immune checkpoint inhibitors†

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Background: There are limited data about the quality of immune-related adverse event (irAE) reporting in immune checkpoint inhibitor (ICI) clinical trial publications.

Methods: A systematic search of citations from Medline, EMBASE and Cochrane databases identified prospective clinical trials involving ICIs in advanced solid tumors from 2003 to 2013. A 21-point quality score (QS) was adapted from the CONSORT harms extension statement. Linear regression was used to identify factors associated with quality reporting.

Results: After a review of 2628 articles, 50 trial reports were included, with ICIs as either monotherapy (54%) or part of a combination regimen (46%). The mean QS was 11.21 points (range 3.50–17.50 points). The median grade 3/4 AE rate reported was 21% (range 0%–66%) and 29/50 (58%) trials concluded that irAEs were tolerable. Multivariate regression analysis revealed that year of publication (within last 5 years, $P = 0.01$) and journal impact factor >15 ($P = 0.004$) were associated with higher QS. Complete reporting of specific characteristics of irAEs including onset, management and reversibility were reported by 14%, 8% and 6% of studies, respectively. The incidence of grade 3/4 adverse events was higher for inhibitors against CTLA-4 compared with other immune checkpoints ($P < 0.001$).

Conclusions: The reporting of irAEs is suboptimal. A standardized reporting method of irAEs that accounts for tolerability, management and reversibility is needed and would enable a more precise evaluation of the therapeutic risk benefit ratio of ICIs.

Key words: adverse event, immune checkpoint inhibitors, quality control, systematic review

introduction

Cancers arise in the context of a dysfunctional immune system. Evasion of host immune responses and tumor-induced immune suppression are important to oncogenesis [1]. Immune checkpoints are inhibitory pathways that modulate immune system activation and can be hijacked to suppress antitumoral T-cell responses. Immune checkpoint inhibitors (ICIs) alleviate tumor-induced immunosuppression of T cells, and thereby enhance antitumor immunity [2].

Recent studies of ICIs reported durable antitumor responses in various tumor types [3–5]. Ipilimumab is a cytotoxic T-lymphocyte antigen-4 (CTLA-4) monoclonal antibody approved by the US Food and Drug Administration for use in advanced melanoma [6]. More recently, the programmed death-1 receptor (PD-1) antibody pembrolizumab obtained accelerated approval for ipilimumab-resistant metastatic melanoma [7]. Registration of other ICIs and additional indications for ICIs is highly anticipated in the near future [8]. Promising activity in other types of cancer have also been demonstrated in several early phase clinical trials investigating either single or combination of ICI agents, with response rates ranging from 20% to ∼50% in patients with advanced melanoma, renal cell carcinoma, head and neck, bladder or lung cancer previously treated with standard therapy [9–11].

Drug-induced autoimmune-like toxicities have been observed in patients treated with ICIs through immune cell infiltration into normal noncancerous tissues. Such effects are not frequently observed with cytotoxic chemotherapy or other classes of targeted agents [12]. These immune-related adverse events (irAEs) can affect multiple organs such as skin, bowel, kidney, peripheral and central nervous system, liver, lymph nodes, eyes, pancreas and endocrine tissues. Their presentation can range from mild and manageable, to severe and life threatening if not recognized early and treated with appropriate measures such as corticosteroids [13].

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Adverse event (AE) reporting in clinical trials is critical for risk-benefit evaluation of a treatment. Substantial variability in AE reporting has been reported in nononcologic clinical trials [14, 15]. Reviews of oncology studies of all phases have shown that AE reporting is typically inadequate [16–18]. The objective of this study was to review the quality of irAE reporting in ICI clinical trials.

methods

study selection

A literature search for prospective clinical trials from 2003 to 2013 of ICIs in solid tumors was conducted in Ovid Medline, EMBASE and Cochrane databases using the keywords neoplasm, clinical trials and immune checkpoint. Specific ICI drug names were also included in the search terms (supplementary Table S1, available at *Annals of Oncology* online). Clinical trials of any phase in adult patients with solid tumors that were published in English were included. Duplicates, abstracts, case reports, case series, correlative studies and secondary reporting of clinical trials were excluded. The search was conducted in November 2013.

quality score for irAE reporting

A 21-point quality score (QS) was adapted from the extension of Consolidated Standards of Reporting Trials (CONSORT) statement for harms reporting [19] (supplementary Table S2, available at *Annals of Oncology* online). Although CONSORT was developed for randomized, controlled trials, the standards for AE reporting are applicable across all types of clinical trials and for all types of AEs. However, irAEs have a unique set of properties and in order to account for this CONSORT was adapted. Items pertinent to irAE reporting include methods of irAE assessment, duration of irAE evaluation, time of onset, management and resolution of irAEs.

There were a total of 22 items in the 21-point QS, addressing different domains of reporting. Twenty of the 22 items had a maximum score of 1 point for complete reporting. Among these, four items in the Results domain could receive 0 points for no reporting, 0.5 point for partial reporting and 1 point for complete reporting. These four items relate to AE grading, time to occurrence, management and resolution. Two of the 22 items had a maximum score of 0.5 points for complete reporting. These two items are in the Discussion domain and are scored if specific statements exist to describe drug tolerability and manageability or reversibility of toxicity. In the Discussion domain, consistency between interpretation and reporting of irAEs was assigned one point. Inconsistency was defined as the article stating irAEs were tolerable when the overall grade 3/4 AE rate was higher than 33% or not reported; or when the authors concluded that irAEs were manageable or reversible without providing any management of these toxicities or without documenting any outcomes of irAEs, respectively. A threshold of 33% was selected to assess the overall tolerability of grade 3/4 AE rates in the reported trials. This assumption is reasonable given that 33% is commonly used as a maximum acceptable frequency for dose-limiting toxicity in early phase trials, although not all grade 3/4 events are dose limiting.

data extraction

All publications that fulfilled the inclusion and exclusion criteria were reviewed in duplicate (TWC and ARH) and disagreements were resolved by consensus. If applicable, the supplementary data, available at *Annals of Oncology* online, were included in the review. Information on study size, journal impact factor (IF), tumor type, randomization, phase of study, ICI target, region of trial and year of publication was extracted. In addition, the incidence of grade 3/4 AEs was collected. The rate of grade 3/4 irAEs was preferentially selected from each study and included AEs of special interest that were immune-mediated toxicities. If irAE frequency could not be determined from the publication, then the rates of grade 3/4 treatment-related AEs (trAEs) regardless of the causal relationship to ICI therapy were extracted.

statistical analysis

The QS was the sum of the score of each item. QS were summarized using descriptive statistics such as mean, confidence interval (CI) and range. Univariate and multivariate linear regressions were carried out to identify factors associated with higher QS. The following trial characteristics were included as variables: ICI target (CTLA-4 versus PD-1/PD-L1 versus other), tumor type (single versus mixed), phase of study (phase I and phase I/II versus not phase I), ICI agent regimen (single ICI versus ICI in combination with other treatment modalities), trial design (randomized versus nonrandomized), sponsor type (industry versus nonindustry), year of publication (2003–2008 versus 2009–2013), the IF of the publishing journal (>15 versus ≤15, based on the IF from Journal Citation Report of year 2012 [20]), presence of supplementary data (yes versus no), trial regions in which the clinical trial was conducted (multinational versus North America versus Europe versus other), and study size (>45 versus ≤45, based on the median number of patients enrolled). Covariates with a $P < 0.15$ in the univariate model were included in the one-step multivariate model. Correlation between the grade 3/4 AE rate and QS were analyzed using Pearson's correlation. Grade 3/4 AE rates and QS were stratified according to the types of AE reported (i.e. irAE versus trAE) and compared using Mann–Whitney *U*-test. A $P \leq 0.05$ was considered statistically significant for all tests.

results

trial characteristics

The search strategy identified 2628 published articles. After review, 50 trials with a total of 5071 patients were selected for analysis (supplementary Figure S1, available at *Annals of Oncology* online). The characteristics of the clinical trials are listed in supplementary Table S3, available at *Annals of Oncology* online. CTLA-4 was the target for the majority ICIs tested in clinical trials (86%), and all publications before the year 2009 were of ICIs targeting CTLA-4. Twenty-three (46%) trials were restricted to patients with melanoma, and 9 (18%) studies were opened to multiple tumor types. Phase I (40%) or I/II (10%) accounted for half of the studies, with a minority of phase III trials (6%). Clinical trials investigating the combination of ICIs with other treatments were common (46%), these included cytotoxic agents (7), vaccines (6), immune modulators (4), molecularly targeted

agents (2), hormonal agents (2), radiation (1) and a combination of two ICIs (1). Twenty (40%) publications, including 9 phase I and 15 nonrandomized clinical trials, were published in high impact journals (IF >15). Twenty-three (46%) articles presented additional information in a supplementary Appendix, available at *Annals of Oncology* online.

the quality score

The overall mean QS was 11.21 (95% CI 10.46–11.96; range 3.50–17.50) (supplementary Figure S2, available at *Annals of Oncology* online). The composite scoring of each item is shown in Figure 1. Items related to the trial methods were often inadequately reported. Overall, five of the six method items were inadequately reported by ≥50% of trial reports. Only 8% of publications explicitly defined in the Methods section how AE attribution was determined and this was the worst reported item. Thirty studies (60%) failed to distinguish irAEs from other organ-system-specific toxicities.

Rates of grade 3/4 AEs were reported by almost all studies (96%). In regards to reporting time to occurrence, management and outcomes of all irAEs or all trAEs, only 7 (14%), 4 (8%) and 3 (6%) studies provided comprehensive accounts of this information, respectively. Partial reporting of these three items was provided by 16 (32%), 35 (70%) and 34 (68%) studies, respectively.

Twenty-nine studies described the investigational regimen as tolerable and 27 studies concluded that the irAEs were manageable and/or reversible. Ten studies did not make any statement regarding tolerability, manageability or reversibility of irAEs in the Discussion section. Discrepancies between the presented results and interpretation of AEs were observed in 11 trials: 17% (5/29) of studies stated that the tested agent or combination was tolerable when the grade 3/4 irAE or trAE rate was >33% or not reported; and 22% (6/27) of studies asserted that the irAEs were reversible or manageable without reporting any toxicity outcomes or AE management, respectively.

types of AE reporting

The median grade 3/4 AE rate was 21% (range 0%–66%). Grade 3/4 irAEs and trAEs were reported in 32 (64%) and 18 (36%) studies, respectively. There was no significant correlation between rates of grade 3/4 AE and QS ($R = -0.03$, $P = 0.84$). In clinical trials of single-agent ICIs, the incidence of overall grade 3/4 AEs was not significantly different between studies using irAEs (median = 19%) and those using trAEs (median = 18%) as the type of AE reporting. However, in trials utilizing combination regimens, studies that reported only trAEs (median = 39%) had a significantly higher overall grade 3/4 AE incidence compared with those using irAEs (median = 23%) ($P = 0.03$) (supplementary Figure S3a, available at *Annals of Oncology* online). In monotherapy trials ($n = 27$), the grade 3/4 AE frequency of CTLA-4-targeting agents was significantly higher than non-CTLA-4-targeting agents ($P = 0.001$) (supplementary Figure S3b, available at *Annals of Oncology* online) but no statistically significant difference was observed in QS for these trials ($P = 0.87$).

univariate and multivariate analysis

Publications within the last 5 years, articles in journals with an IF over 15, trials that enrolled a single tumor type, and study population sizes over 45 patients were factors associated with higher QS in the univariate model ($P < 0.15$). Given that before 2009 only papers of CTLA-4 ICIs were published, the impact on QS by ICI targets other than CTLA-4 may be confounded by the year of publication. Hence, a univariate analysis of ICI targets (CTLA-4, PD-1, PD-L1 and LAG3) was carried out limited to the years 2009–2013. This demonstrated that ICI drug target did not affect QS during this period ($P = 0.79$ for PD-1/PD-L1; $P = 0.32$ for LAG-3 and PD-1/CTLA-4 combination). The only factors that were significantly associated with higher QS for irAE reporting were publications in the last 5 years ($P = 0.01$) and high IF journals ($P = 0.004$) (Table 1) in the multivariate analysis. Inclusion of supplementary data did not correlate with an improved QS ($P = 0.21$).

discussion

Promising antitumor activity has been observed with ICIs. Current guidelines for side-effect assessment, such as Common Terminology Criteria for Adverse Events (CTCAE) have not been designed for irAE reporting and thus its utility in this area is uncertain. Efforts to present associated toxicities accurately are needed to ensure balanced reporting. Several reviews of clinical trials of molecular targeted and chemotherapeutic agents have found that harms are often underreported in oncology trials [15–18, 21]. This is the first systematic review to demonstrate that the quality and completeness of irAE reporting in ICI trials is suboptimal and heterogeneous. Quality of reporting improved over time, which may reflect growing recognition and familiarity among investigators with unique features of irAEs. Journals with an IF over 15 were associated with better reporting standards of ICIs. Increased rigor of editorial review and more stringent publication requirements of high IF journals may account for these differences. Other factors, such as trial phase, tumor types and study sample size were not correlated with reporting quality.

The QS applied in this study was adapted from the extension of the CONSORT statement of harms and a previously developed 16-point oncology specific AE-reporting score [17]. Factors pertinent to the assessment of toxicities-related ICIs such as timing, reversibility and management were specifically incorporated into the QS. Unlike the 16-point scoring system that only scores 0 or 1 for each item, the QS used in this review assigned half points for partial reporting. Although word limits in journal publications limit the ability of authors reporting ICI studies to address all items in the 21-point QS, attempts should be made to report at least the time to onset, duration, management and reversibility of all grade 3/4 irAEs. Other items could be presented in full detail as part of a supplementary Appendix, available at *Annals of Oncology* online. The assessment of QS was based on review of the full trial publication including any supplementary Appendices, available at *Annals of Oncology* online, but the presence of a supplementary Appendix, available at *Annals of Oncology* online did not correlate with a higher QS.

Description of the methods used to assess ICI toxicity in trial publications was notably poor. Decisions to attribute causality are complex, which may explain why they were often not reported. Nevertheless, attribution is important especially when ICIs were combined with other treatments. The duration of

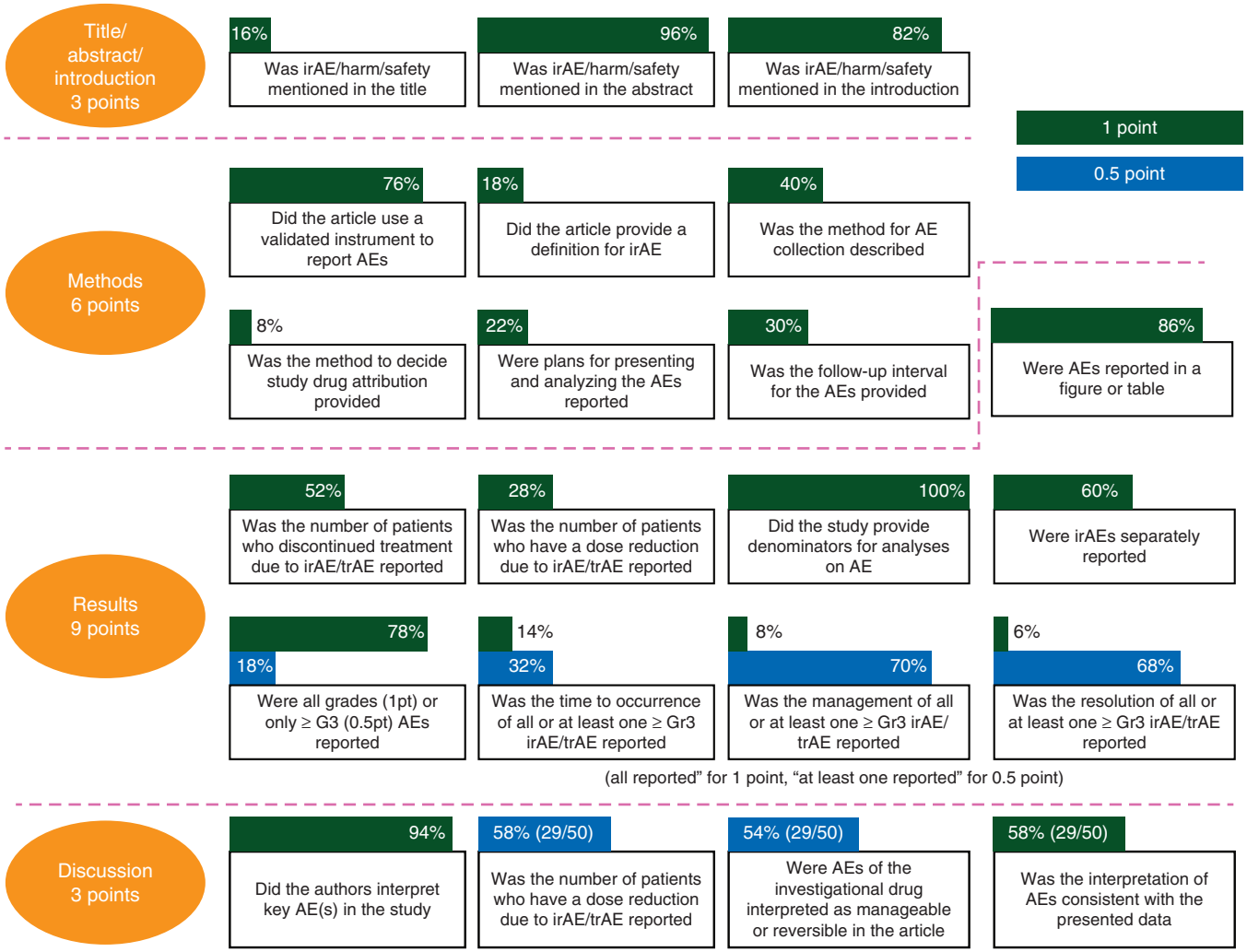

Figure 1. Components of the 21-point quality score and the scoring of each item from the 50 clinical trials. Items only reported as treatment-emergent adverse events were scored 0 points. irAE(s), immune-related adverse event(s); trAE(s), treatment-related adverse event(s).

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Table 1. Univariate and multivariate regression analyses of factors associated with quality score

Study characteristic	Quality score	Linear regression			
		Univariate analysis		Multivariate analysis	
	Mean	Coefficient	*P* value	Coefficient	*P* value
ICI target					
CTLA-4	11.22	Ref		NA	NA
PD-1/PD-L1	11.63	0.40	0.78		
Others	10.50	−0.65	0.66		
Tumor type					
Mixed	9.94	Ref		Ref	
Single	11.49	1.54	0.11	1.13	0.21
Phase of study					
Not phase I	11.66	Ref		NA	NA
Phase I	10.76	−0.90	0.23		
ICI agent regimen					
Combination	11.67	Ref		NA	NA
Single agent	10.81	−0.86	0.26		
Randomized					
No	11.02	Ref		NA	NA
Yes	11.95	0.93	0.33		
Source of trial funding					
Nonindustry	11.33	Ref		NA	NA
Industry	11.19	−0.14	0.91		
Year of publication					
2003–2008	9.09	Ref		Ref	
2009–2013	11.81	2.71	0.002	2.12	0.01
Journal impact factor					
≤15	10.27	Ref		Ref	
>15	12.63	2.36	0.001	2.20	0.004
Supplementary data					
No	10.78	Ref		NA	NA
Yes	11.72	0.94	0.21		
Region in which trials were conducted					
Multinational	12.05	Ref		NA	NA
North America	10.98	0.80	0.57		
Europe	11.25	−0.27	0.83		
Other	10.00	−1.25	0.67		
Trial patient number					
≤45	10.60	Ref		Ref	
>45	11.82	1.22	0.10	−0.14	0.84

CTLA-4, cytotoxic T-lymphocyte antigen-4; ICI, immune checkpoint inhibitor; NA, not applicable; PD-1, programmed death-1; PD-L1, programmed death ligand 1; Ref: reference.

follow-up for irAEs is also infrequently reported (30%). As irAEs may continue to evolve even after drug treatment is discontinued, it is critical to have an adequate time for follow-up of irAEs and to evaluate resolution or persistence of toxicities [22]. While most drug-related AEs are considered reversible after discontinuation, the mechanism of irAEs may lead to persistent symptoms or worsening severity when ICIs are stopped. Duration of follow-up for such toxicities may be complicated if patients start another therapy following discontinuation of ICI treatment [23].

Significant discrepancies between AE interpretation and the reported safety results of irAEs were identified. Seventeen percent of studies over stated the safety of the experimental regimen. These conclusions give an impression that these agents have minimal or few toxicities, when actually a considerable proportion of patients experienced a severe AE. Concerns about bias in the reporting of toxicities in clinical trials with a positive primary end point have previously been raised [24]. Furthermore, around one-fifth of articles suggested that toxicities did not persist or were readily manageable, without presenting any data or evidence to support this claim. Such incomplete reporting may lead to a skewed representation of the tolerability of a novel ICI regimen.

In trials of combination regimens, the incidence of grade 3/4 AEs were significantly higher if reported as trAEs when compared with those reported as irAEs. This is not surprising given that multiagent treatments may produce unpredictable AEs or overlapping toxicities, such as the high rates of hepatotoxicity that have been observed from the combination of ipilimumab

and vemurafenib in patients with metastatic melanoma [25]. Furthermore, authors may prefer to use trAE reporting because it covers both immune and nonimmune side-effects. Nevertheless, the true frequency of irAEs in multiagent clinical trials cannot be known when reported as trAEs. Distinguishing between irAEs and trAEs in combination regimens is a complex task given uncertainties with toxicities from nonimmune therapies and the potential for drug interactions, but it is also important to make this distinction because management of irAEs may be different from trAEs. In addition, it enhances the understanding of the toxicity profile of the experimental regimen. The distinction between irAEs and trAEs may be less relevant for trials of single-agent ICI because authors may be more comfortable attributing toxicities to the immunological activity of the agent.

There are several limitations of our study. The conclusions must be interpreted in the context of the relatively small number of trials that were included with modest sample sizes. Caution should be taken when applying the QS to other types of immune treatments such as immunostimulatory molecules, cytokines, oncolytic viruses, vaccines, tumor-infiltrating lymphocytes and adoptive cell or gene transfer, as it has not been applied to non-ICI immunotherapy trials. Subjectivity in patient description and clinician assessment of toxicities will also affect irAE interpretation and thus reporting. To address this, standardized patient-reported tools to evaluate the impact of irAEs from ICIs on health-related quality of life should be developed, similar to a functional assessment of chronic illness therapy questionnaire such as FACT-EGFR-18 for dermatologic toxicities from epidermal growth factor receptor inhibitors [26].

This systematic review demonstrates that reporting of irAEs has improved over the last 5 years, although it is still often incomplete. We do not propose to amend current systems for classifying AEs for example the CTCAE, as these were intended to capture side-effects and not guide toxicity reporting. Instead a standardized reporting method of irAEs that accounts for tolerability, management and reversibility is needed to ensure completeness and transparency of published trial data. This would enable a more precise evaluation of the therapeutic risk-benefit ratio of ICIs. Authors should consider using the 21-point QS system to guide reporting of harms in presentations or manuscripts of trials involving ICIs.

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disclosure

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