ClinicalTrials.gov for Facilitating Rapid Understanding of Potential Harms of New Drugs: The Case of Checkpoint Inhibitors

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New drugs, particularly those belonging to novel drug classes, can dramatically improve clinical outcomes but may also lead to serious toxicities. Given an emphasis on disease outcomes, drug-related toxicities may go unrecognized for years[1-6] or be subject to biased reporting,[7] and rarer toxicities may emerge during postmarketing surveillance.[8,9] Delayed toxicity recognition in rapidly adopted drugs can impede clinicians' ability to weigh potential drug benefits against harms and lead to unintended patient harm.[10] A 2016 National Cancer Policy Forum workshop on drug development emphasized balancing the benefits and harms of new drugs, noting that poor knowledge of adverse events limits risk-benefit modeling.[11] Optimizing accuracy and transparency of toxicity reporting in clinical trials and facilitating pooling of these data across studies would enable earlier understanding of toxicities, protect patients, and facilitate risk-benefit modeling.[8] Ongoing efforts to more rapidly identify toxic drug effects have not leveraged data available on ClinicalTrials.gov.

The ClinicalTrials.gov Web site was created to improve transparency, patient access to clinical trial information, and evidence quality.[12,13] The US Food and Drug Administration (FDA) Amendments Act established the legal mandate, and the 2016 Final Rule clarified reporting requirements, including provision of information about drug toxicities in the form of adverse events.[13,14] Although primarily designed to improve transparency regarding outcomes, ClinicalTrials.gov also has the potential to facilitate understanding of toxicities of new drugs. However, the FDA mandates no specific reporting terminology, and lack of uniformity coupled with poor-quality adverse event data[15] could hinder pooling of these data across trials.

Checkpoint inhibitors are important new drugs, the toxicities of which are not fully understood.[16] They can dramatically improve clinical outcomes across cancers but may lead to serious immune-mediated toxicities affecting any organ.[17-21] Delayed recognition of toxicities could lead to patient harms.[10] Although published clinical trial reports include descriptions of common and severe toxicities, published toxicity data tend to be incomplete and focus on expected complications; reliable data sources are needed to enable timely understanding of previously unrecognized toxic effects. We explored the consistency of adverse event terminology reported on ClinicalTrials.gov in clinical trials of checkpoint inhibitors, a paradigm of a new potentially revolutionary drug class, to evaluate opportunities for data pooling.

We extracted adverse event information from ClinicalTrials.gov and found wide-ranging terminology, posing challenges to the pooling of toxicity data and understanding of the potential harms of this new drug class. In this editorial, we draw

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attention to how the current system of adverse event reporting on ClinicalTrials.gov represents a missed opportunity to enhance early understanding of the potential harms of new classes of cancer therapy.

Variability in Adverse Event Reporting

We present the scope of adverse events reported by randomized clinical trials (RCTs) of checkpoint inhibitors that reflect four immune-mediated toxicities: colitis, dermatitis, hepatitis, and thyroiditis.[17-19,22] We systematically searched PubMed to identify published phase II/III RCTs of checkpoint inhibitors with full trial results posted on ClinicalTrials.gov by December 9, 2016 (Table 1). We generated a list of descriptive adverse event terms from ClinicalTrials.gov that might reflect each toxicity, categorizing them as symptoms (patient-reported clinical problems), signs (clinician-detected abnormalities), abnormal test results, or diagnoses (defined clinical entities; Table 2). For each toxicity, we determined the number of trials reporting each term. We included any term reported as either a serious or other adverse event on ClinicalTrials.gov.

Our search identified 325 studies; we extracted data from 20 studies representing 15 RCTs. Most trials (n = 15) reported adverse events using MedDRA (Table 1); all trials collected data using Common Terminology Criteria for Adverse Events. Study drugs included ipilimumab, nivolumab, nivolumab and ipilimumab, and pembrolizumab (Table 1).

The number of descriptive terms ranged from eight for thyroiditis to 24 for colitis (Table 2). For all four toxicities, terms from at least three of the four categories were reported by at least one trial, and few terms were included across all trials. For colitis, all trials used the terms abdominal pain, constipation, and diarrhea; other terms varied. For dermatitis, all trials reported pruritis (n = 15); most reported rash (n = 14). For hepatitis and thyroiditis, 14 trials reported at least one adverse event term, most often a diagnosis or test result.

Limitations of Current Adverse Event Reporting

Checkpoint inhibitors are being rapidly adopted into clinical practice; reliable data sources are needed to capture and understand their toxicities. Given researcher comfort with traditional chemotherapy, and because toxicities are often immediate and dose related, potential chemotherapy toxicities are easily recognized during clinical trials. However, new drug classes may differ, so mechanisms for enhancing recognition of toxicities are needed to protect patient safety. In the case of checkpoint inhibitors, we found that ClinicalTrials.gov included multiple terms potentially representing select toxicities, sometimes including symptoms, signs, diagnoses, and laboratory results with inconsistency across trials. These inconsistencies limit our ability to understand the prevalence of toxicities and pool data across trials, hindering the power of ClinicalTrials.gov to meaningfully enhance the safety of patients with cancer.

Currently, adverse event reporting on ClinicalTrials.gov does not enable determination of the total number of patients experiencing a given toxicity, because reporting of a single toxic event might use multiple terms across domains (eg, including

Table 1. List of Included Trials and Corresponding Studies

Trial No.	Study Represented	Checkpoint Inhibitor Studied	Source Term*
NCT01673867	Borghaei[23] 2015	Nivolumab	MedDRA 17.1
NCT01642004	Brahmer[24] 2015	Nivolumab	MedDRA 17.1
NCT00636168	Eggermont[25] 2016 Eggermont[26] 2015	Ipilimumab	MedDRA 16.1
NCT01927419	Hodi[27] 2016 Postow[28] 2015	Nivolumab, ipilimumab (concurrently)	MedDRA 17.0
NCT01134614	Hodi[29] 2014	Ipilimumab	CTCAE 4.0
NCT00094653	Hodi[30] 2010 McDermott[31] 2013 Robert[32] 2013	Ipilimumab	MedDRA 12.1
NCT00861614	Kwon[33] 2014	Ipilimumab	MedDRA 18.0
NCT00527735	Lynch[34] 2012 Reck[35] 2013	Ipilimumab	MedDRA 13.0
NCT01668784	Motzer[36] 2015	Nivolumab	MedDRA 18.0
NCT01354431	Motzer[37] 2015	Nivolumab	MedDRA 16.0
NCT01450761	Reck[38] 2016	Ipilimumab	MedDRA 18.0
NCT01721772	Robert[39] 2015	Nivolumab	MedDRA 17.0
NCT01866319	Robert[40] 2015	Pembrolizumab	MedDRA 17.0
NCT00324155	Robert[41] 2011	Ipilimumab	MedDRA 16.1
NCT01783938	Weber[42] 2016	Nivolumab, ipilimumab (sequentially)	MedDRA 18.0

*Source terms represent the terminology dictionary used to report adverse events on ClinicalTrials.gov.

Table 2. Terms of Adverse Events Consistent With Selected Toxicities and Their Frequency of Reporting Among Clinical Trials

Toxicity (No. of trials)*	Symptom (No. of trials)†	Sign (No. of trials)†	Diagnosis (No. of trials)†	Test Result (No. of trials)†
Colitis (15)	Abdominal discomfort (1)	Abdominal distension (9)	Colitis (15)	GI perforation (2)
	Abdominal pain (15)	Colonic hemorrhage (1)	Colonic perforation (2)	Pneumoperitoneum (1)
	Abdominal pain lower (5)	Diarrhea hemorrhagic (2)	Duodenal perforation (1)	
	Constipation (15)	GI hemorrhage (9)	Enterocolitis (7)	
	Diarrhea (15)	Lower GI hemorrhage (3)	Enterocolitis hemorrhagic (1)	
	GI pain (2)	Intestinal hemorrhage (2)	Enterocolitis hemorrhagic (1)	
			GI disorder (2)	
			Ileal perforation (1)	
			Intestinal perforation (5)	
			Large intestine perforation (6)	
Dermatitis (15)	Pruritis (15)	Dermatitis acneiform (3)	Erythema multiforme (2)	
	Rash (14)	Dermatitis exfoliative (1)		
	Rash pruritic (3)	Erythema (6)		
		Rash acneiform (1)		
		Rash erythematous (2)		
		Rash generalized (1)		
		Rash macular (2)		
		Rash maculopapular (8)		
Hepatitis (14)	Hepatic pain (1)		Acute hepatic failure (1)	ALT increased (13)
			Autoimmune hepatitis (6)	AST increased (12)
			Hepatic failure (5)	LFT abnormal (6)
			Hepatitis (8)	Hepatic function abnormal (3)
			Hepatitis acute (3)	Hepatic enzyme increased (2)
			Hepatocellular injury (5)	Transaminases increased (4)
			Hepatotoxicity (7)	
Thyroiditis (14)		Goiter (2)	Autoimmune thyroiditis (4)	Blood TSH decreased (1)
			Hyperthyroidism (5)	Blood TSH increased (2)
			Hypothyroidism (13)	Thyroid function test abnormal (1)
			Thyroiditis (2)	

Abbreviations: LFT, liver function test; TSH, thyroid-stimulating hormone

*No. of trials that reported at least one of the selected adverse event terms consistent with the toxicity.

†No. of trials that reported the adverse event as either a serious or other adverse event on ClinicalTrials.gov.

both symptoms and diagnoses), obscuring the number of individuals represented. At the same time, many descriptive terms are nonspecific. For example, colitis might be reported under diarrhea, abdominal pain, and/or colitis; however, diarrhea or abdominal pain could be unrelated to colitis. This overlap and poor specificity may relate to the inclusion of

multiple terms that capture a single clinical problem in clinical trial case report forms, limiting transparency and accurate estimates of the prevalence of toxicities.

Policy Implications

There are other potential methods for aggregating toxicity information, including systematic reviews of published toxicity data and FDA pharmacovigilance databases[43]; however, the public nature of ClinicalTrials.gov and its use during initial clinical trials enable early and complete compiling of information. Changes to ClinicalTrials.gov policy could help optimize its usefulness for understanding toxicities. The FDA Amendments Act and the 2016 Final Rule recognized the importance of capturing all-cause mortality, requiring trials to report all-cause deaths without mandating reporting of other specific outcomes.[44] The FDA could establish standards for reporting of the number of patients experiencing specific toxicities, perhaps those that are most severe or most common, for use across all trials of a particular class of drugs, such as checkpoint inhibitors, and/or facilitate public access to narrative descriptions of these toxicities. Alternatively, the oncology research community could describe specific toxicities of interest for public reporting of clinical trials of particular drugs, which would be easy to quickly implement and would avoid political challenges while still leveraging the potential of ClinicalTrials.gov. Either approach would improve reporting clarity and facilitate pooling across trials to elucidate the true prevalence of toxic drug effects, complementing calls for better mechanisms of sharing clinical trial data[45] and efforts to optimize ClinicalTrials.gov.[46]

Comparability of adverse event reporting across trials requires shared language and definitions. Currently, trials reporting on ClinicalTrials.gov can use different dictionaries with vague or variable definitions of specific terms, although primary data are collected using Common Terminology Criteria for Adverse Events. The FDA rule opted against implementing a standard vocabulary, recognizing the potential burden on researchers.[44] However, the lack of standard terminology is a barrier to aggregation and data compilation. Thus, despite potential burden, a standard lexicon for adverse event reporting would benefit researchers, clinicians, and the public and would help ensure patient safety. This lexicon could be developed for specific drug classes to ensure relevance, with toxicity classification using syndrome-specific checklists. In addition, redundancy of reporting could be addressed by requiring reporting of a toxicity in a single patient in only one domain, facilitated by electronic reporting of adverse events. The electronic system could recognize groups of symptoms to define syndromes of interest, prompting the investigator to consider a unifying diagnosis that would then be reported. Such a system might also pull from standard electronic medical records, reducing reporting burden. Alternatively, programming could capture the evolution of adverse events. For example, for a patient who has diarrhea eventually confirmed as colitis, investigators could be prompted to relabel the diarrhea as early colitis if appropriate rather than reporting both as adverse events.

In conclusion, novel drug classes have the potential to dramatically improve outcomes in patients with cancer, but rapid understanding of their toxicities is critical. Although ClinicalTrials.gov has the potential to facilitate more complete understanding of toxicities, the wide-ranging terminology in current use impedes transparency and possibly patient safety. A standard vocabulary, required reporting for select adverse events, and electronic systems to identify syndromes and optimize reporting would clarify data, allow better estimates of toxicity rates, and facilitate pooling of toxicity data across trials. In this way, investigators and clinicians could better understand potential patient harms and optimize safety for patients receiving potentially lifesaving, but also potentially toxic, therapies. JOP

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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