Is There Room for Improvement in Adverse Event Reporting in the Era of Targeted Therapies?

Maureen Edgerly, Tito Fojo

Clinical toxic effects resulting from targeted therapies present a challenge for our currently available adverse event coding system because of the subacute nature of the toxic effects that are experienced over prolonged periods of daily drug administration. The case of mitotane (1) (Lysodren; Bristol Laboratories Oncology Products), which was approved by the Food and Drug Administration (FDA) in 1970 for the treatment of inoperable adrenal cortical carcinoma, illustrates the limitations of the Common Terminology Criteria for Adverse Events (CTCAE), version 3.0 (2), in coding adverse events associated with anticancer agents (see Box 1 for definitions of terms). Mitotane serves as an example for some of the “targeted” therapies now under development in that it is administered orally, often in divided doses, for prolonged periods of time, either as a single agent or in combination with other anticancer agents. Importantly, although this drug rarely causes toxic effects that are more severe than grade 2 (or, for that matter, even grade 1), it is despised by patients, nearly all of whom realize how poorly they felt while taking mitotane after they discontinue its use. The side effects of mitotane can be protean but are most commonly characterized by nausea without vomiting, which often results in gradual weight loss, diarrhea, malaise, and detrimental changes in mental status.

The need for frequent dose reductions and treatment interruption as administration of mitotane continues over time, together with the occasional observation that a patient who claims to be complying with a prescribed dose has very low or undetectable serum levels of mitotane, even after months of administration, underscore the inadequacy of the CTCAE as a coding system for adverse event reporting for agents that are intended to be administered daily and for long times. The CTCAE was developed in an era when most anticancer agents were administered intermittently and had toxic effects that were transient in nature. Whereas a grade 1 or 2 diarrhea that lasts 1 or 2 days is generally well tolerated by most patients, a grade 1 or 2 diarrhea that continues for months is not. Patients may find this latter situation intolerable, and clinical research professionals must be able to code (ie, grade) and report such events appropriately. But what is appropriate in this situation?

Table 1 lists the criteria for grading diarrhea as reported on page 20 of the CTCAE (2). Note that for both grades 2 and 3, the final clause refers to the impact of the diarrhea on a patient’s activities of daily living (ADL). But how do we define “intolerable” in relation to a drug’s effects on ADL? Is “intolerable to a patient” the same as “interfering with ADL”? What about adverse events that do not contain the ADL stipulation, such as nausea and vomiting (Table 2)?

The purpose of this commentary is to argue that for physicians and clinical research staff to understand and properly assess, code (ie, grade), and report the toxicity of a new agent and compare new therapies against those already accepted, the current criteria (ie, the CTCAE) and reporting mechanisms must be partially revised.

Federal regulations allow trial sponsors to decide how frequently and in what manner the investigators will report routine, nonserious adverse events (4). Sponsors establish standard operating procedures and investigators comply with these procedures on a study-specific basis. Consequently, it is not surprising that not all studies are reported in the same manner or are published in a format that allows health-care providers to adequately compare the adverse events associated with different therapies. For example, the National Cancer Institute (NCI) Cancer Therapy Evaluation Program (CTEP) has adverse event reporting requirements that apply to studies sponsored by the NCI (5). These guidelines clearly define terminology, designate the CTCAE as the grading scale to be used, and refer investigators to the Comprehensive Adverse Event and Potential Risks, which is a complete list of the reported and/or potential adverse effects associated with each agent under a CTEP
investigational new drug application. Importantly, these guidelines differentiate the reporting requirements for phase 1 trials from those for phase 2 and phase 3 studies as well as routine from expedited reporting. These guidelines also address reporting requirements for persistent and/or recurring adverse events. According to the CTEP guidelines, a persistent adverse event “is one that extends continuously, without resolution between cycles/courses.” For both routine and expedited reporting, it adds, “The event must only be reported once unless the grade becomes more severe…” It further adds that a recurring adverse event “is one that occurs and resolves during a cycle/course of therapy and then reoccurs in a later cycle/course.” These recurring events must be reported for each cycle in which they recur. Clearly, according to these guidelines, an adverse event that persists unabated for several cycles is being underreported or at least underrepresented in a data summary.

How should we reasonably account for ongoing grade 1 and 2 adverse events, particularly the clinical (ie, nonlaboratory) grade 1 and 2 adverse events that become intolerable to a patient? Whereas the occurrence of grade 3 and 4 events appropriately triggers treatment modifications, the occurrence of grade 1 and 2 events that persist for weeks or longer does not meet most protocol criteria for dose reductions. However, these persistent and recurrent events may understandably result in poor compliance, dose reductions, or refusal by the patient to continue therapy. We contend that grade 1 or 2 adverse events that incur a dose reduction or interruption or that cause a patient to discontinue therapy should be reported in a manner more representative of their outcome.

Because the CTCAE definition of many, but not all, grade 3 events includes the clause “interfering with activities of daily living (ADL),” we propose that a grade 2 event that prompts a patient to discontinue therapy even briefly or that motivates the health-care provider to reduce the dose could be classified in a manner that quantifies this severity given that that such adjustments were most likely needed because the therapy interfered with ADL. In other words, grading of adverse events should be based not solely on the outward symptoms (episodes of diarrhea or emesis) but rather on all the unique descriptions of severity within each adverse event, including the effects on ADL.

In this regard, we note that the current definitions of ADL and instrumental ADL (IADL; Box 1) do not take into account the high level of functioning of many patients who continue to work while they receive therapy. For example, consider a patient who has been working full time but finds it necessary to reduce his hours because he has been experiencing diarrhea four or five times per day, often while at work. According to the current definitions of ADL and IADL, the patient is still able to eat, dress, shower, live independently, prepare his own meals, manage his money, shop, do housework, and use a telephone. Although the four to five episodes of diarrhea per day do not interfere with his ADL as they are not viewed as interfering with his daily routine. Perhaps the definitions of ADL and IADL should also be examined to account for the adverse effects of daily therapies with more prolonged toxic effects.

Complete data on adverse events include the grade and attribution as well as the duration of the adverse event and the need for intervention or other variables that impact the subject’s participation in the study. Because the latter two factors are intimately related to a drug’s safety evaluation, we argue that grading and/or reporting of toxicity should be amended to adequately reflect these two factors. For example, Table 2 lists criteria for grading nausea and vomiting as reported on pages 24 and 28, respectively, of the CTCAE (2). We maintain that a patient who experiences grade 2 nausea and vomits two or three times per day for 6 weeks is experiencing a toxicity that should be graded as something more than grade 2.

Although one could argue that the current CTCAE and CTEP reporting guidelines help to identify safe doses, they in fact only identify the dose a patient can tolerate for a brief period of time.

Box 1. Glossary of terms

**Activities of daily living (ADL)** (3): The tasks of everyday life. Basic ADL include eating, dressing, getting into or out of a bed or chair, taking a bath or shower, and using the toilet. Instrumental ADL (IADL) are activities related to independent living and include preparing meals, managing money, shopping, doing housework, and using a telephone (also called activities of daily living).

**Coding:** Assignment of codes (grades) to adverse events using the Common Terminology Criteria for Adverse Events, version 3.0.

**Documentation:** Notes and/or data in a medical record that serve as a source document.

**Publishing:** Study reports published in a peer-reviewed journal or a product monograph.

**Recording:** Data in a clinical trials database, a specific subset of the fully documented record.

**Reporting:** Data, including coded adverse events, transferred from a clinical trials database to a sponsor or from a sponsor to the Food and Drug Administration.

---

Table 1. Common Terminology Criteria for Adverse Events, version 3.0: diarrhea*

<table>
<thead>
<tr>
<th>Grade 1</th>
<th>Increase of &lt;4 stools per day over baseline; mild increase in ostomy output compared with baseline</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 2</td>
<td>Increase of 4–6 stools per day over baseline; IV fluids indicated ≥24 h; moderate increase in ostomy output compared with baseline; not interfering with ADL</td>
</tr>
<tr>
<td>Grade 3</td>
<td>Increase of ≥7 stools per day over baseline; incontinence; IV fluids ≥24 h; hospitalization; severe increase in ostomy output compared with baseline; interfering with ADL</td>
</tr>
<tr>
<td>Grade 4</td>
<td>Life-threatening consequences (eg, hemodynamic collapse)</td>
</tr>
<tr>
<td>Grade 5</td>
<td>Death</td>
</tr>
</tbody>
</table>

*ADL = activities of daily living; IV = intravenous.
often with the support of enthusiastic investigators. In an era when the number of me-too drugs (ie, drugs that are structurally similar to known drugs) will likely increase, it will be important for clinical trials to accurately capture and report toxic effects if the FDA is to adhere to its mandate to approve drugs that are either more efficacious or with comparable activity but less toxicity than those already approved. The FDA’s recent guidance document for industry (6) describes how the endpoints for cancer drug approval shifted from objective response rate in the 1970s to improvements in survival, quality of life, physical functioning, and tumor-related symptoms in the 1980s to the current use of established surrogate endpoints for clinical benefit, including disease-free survival. These current endpoints often apply to targeted therapies and should predict clinical benefit (that is, the new drugs should provide a benefit compared with currently available therapy). If the FDA is basing approval decisions on this criterion of disease-free survival, then it is imperative that the reported data accurately reflect the long-term effects of a drug on physical functioning, quality of life, and tumor-related symptoms, in addition to its effects on disease-free survival.

Another issue of concern is the determination of maximally tolerated dose for oral agents that are administered for prolonged times. The maximally tolerated dose is historically defined by toxic effects that occur during the first cycle of treatment (or during the first 4–6 weeks for oral agents taken daily). However, with daily oral agents, many dose-limiting toxic effects will not be captured and reported because they occur weeks to months after the initiation of drug administration and after the defined period of the maximally tolerated dose determination has passed (neurotoxicity with taxanes is an historical example of such a late-occurring dose-limiting toxic effect). We propose that a second maximally tolerated dose be established for daily agents, one that accurately captures the experiences of patients who take the agent for the recommended 3 months or longer. We also propose that efficacy be based on this second maximally tolerated dose, which represents the dose that many patients will actually receive.

The adverse events reporting plan should also reflect the proposed length of drug administration. Although it is important to know the toxic effects during the first cycle (however that is defined), it is equally important to know the long-term, cumulative toxic effects that are likely to occur with the suggested labeled dosing. Community physicians should not be tasked with “discovering” these toxic effects independently, particularly when the data have been documented in clinical trials but not coded, recorded, reported, or published as rigorously as they could have been.

We propose the following revision of the CTCAE that, at a minimum, applies to drugs whose administration is intended to be daily and prolonged (ie, longer than 12 weeks). Grade 2 adverse events would be defined according to the current definition. A grade 2 event that is intolerable to the patient or results in a dose adjustment would be considered to be grade 2A and a grade 2 event that persists continuously for longer than 4 weeks would be considered to be grade 2B.

We hope this commentary will stimulate thoughtful discussion about ways to improve the coding, reporting, and publication of clinical research findings.

Table 2. Common Terminology Criteria for Adverse Events, version 3.0: nausea and vomiting*

<table>
<thead>
<tr>
<th>Grade 1</th>
<th>Grade 2</th>
<th>Grade 3</th>
<th>Grade 4</th>
<th>Grade 5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea</td>
<td>Loss of appetite without alteration in eating habits</td>
<td>Oral intake decreased without significant weight loss, dehydration, or malnutrition; IV fluids indicated &lt;24 h</td>
<td>Inadequate oral caloric or fluid intake; IV fluid, tube feedings, or TPN indicated ≥24 h</td>
<td>Life-threatening consequences</td>
</tr>
<tr>
<td>Vomiting</td>
<td>1 episode in 24 h</td>
<td>2–5 episodes in 24 h; IV fluids indicated &lt;24 h</td>
<td>≥6 episodes in 24 h; IV fluids or TPN indicated ≥24 h</td>
<td>Life-threatening consequences</td>
</tr>
</tbody>
</table>

* IV = intravenous; TPN = total parenteral nutrition.

References

Note
Manuscript received September 5, 2007; revised December 19, 2007; accepted December 20, 2007.