

# Identifying and reporting adverse drug events in oncology

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Protect your patients with updates on adverse events related to various cancer treatments.

In determining whether or not to report an adverse drug event (ADE) to the US Food and Drug Administration (FDA) or other regulatory body, it's important to first establish the cause of the event. Adverse events may be caused by the exacerbation of an existing problem, a side effect, medication error, or an adverse drug reaction (ADR). A drug may be considered the cause of the event if the event would not have occurred without the drug, if the drug resulted in the event occurring sooner than normal, or if the drug amplified the severity of the event.

Without details and careful documentation, it can be difficult to properly diagnose the event and monitor recurrences. Thus, it is imperative that oncologists and nurses take extra care to record in a patient's medical charts any adverse events likely to have been caused by a drug. It is then necessary to distinguish between an ADE and an ADR. An ADE is defined as harm caused by the misuse of a drug, whereas an ADR is harm that results despite having used the drug appropriately. ADEs are preventable events.<sup>1</sup> Although potentially serious, these events, as well as events consistent with the product label, need not be reported to regulatory bodies.<sup>2</sup>

A scale should be used to classify

the likelihood of a suspected ADR.<sup>3</sup> As defined by Edwards and Aronson,<sup>3</sup> suspected ADRs should be classified according to a four-tiered system, ranging from "certain" to "probable," "possible," and "unlikely" based on evidence and timing.

*An ADR may be defined as certain if:*

- The time frame of the reaction can plausibly be linked to the drug;
- The patient responds positively to the removal of the drug;
- A rechallenge results in the re-appearance of the initial reaction.

*An ADR may be defined as probable if:*

- No rechallenge information is available.

*An ADR may be defined as possible if:*

- Its time frame is reasonably related to the administration of the drug in question;
- Its occurrence might also be the result of other drugs or diseases.

*An ADR may be defined as unlikely if:*

- Other chemicals, drugs, and diseases provide likely explanations.

MedWatch, the FDA's safety information and adverse event reporting program, notes that all serious adverse events should be reported. According to MedWatch, a serious adverse event is defined as being one that is life-threatening, requires hospitalization, results in a disability or congenital defect, requires action to avoid permanent impairment or damage, or results in death.<sup>9</sup>

## Fast Facts

ADVERSE DRUG EVENTS (ADEs) and adverse drug reactions (ADRs) are a significant source of morbidity and mortality among cancer patients. ADRs account for more than 100,000 deaths in the United States annually.<sup>4</sup>

There are a number of reasons why efforts to rapidly report ADRs are hampered:

- In oncology, ADRs are particularly difficult to identify and distinguish from tumor progression or comorbidity.<sup>5</sup>
- There is a high rate of off-label drug use in settings for which drug safety profiles have not been sufficiently studied.
- Efforts by drug manufacturers, the US Food and Drug Administration (FDA), and academic organizations are often uncoordinated, inefficient, and under-regulated.
- There are conflicts of interest between sponsors and investigators.<sup>6</sup>
- FDA funding is insufficient.<sup>7</sup>
- The time lag between drug approval and ADR identification and dissemination is tremendous; only half of all serious ADRs are detected and then reported in the *Physicians' Desk Reference* by the seventh year of approval.<sup>8</sup>

**To submit a report**, go to the MedWatch database online at [www.fda.gov/medwatch/](http://www.fda.gov/medwatch/). There you can find information on ADEs and reactions as well as the protocol for submitting a report. To report directly to the RADAR project, contact Dr. Charles L. Bennett at [cbenne@northwestern.edu](mailto:cbenne@northwestern.edu).

**TABLE 1**

ADRs identified by the RADAR project and the number of ADR reports contained in RADAR databases

| Drug                                       | ADR                        | Number of reports in RADAR database |
|--------------------------------------------|----------------------------|-------------------------------------|
| Sirolimus/paclitaxel-coated cardiac stents | Thrombotic events          | 139                                 |
|                                            | Hypersensitivity reactions | 6                                   |
| G-CSF/GM-CSF                               | AML and MDS                | 16                                  |
| Epoetin/darbepoetin                        | Venous thromboembolism     | Meta-analysis                       |
| Thalidomide/lenalidomide                   | Venous thromboembolism     | Meta-analysis                       |
| Epoetin alfa                               | Pure red-cell aplasia      | 9                                   |
| Clopidogrel                                | TTP                        | 13                                  |
| Ticlopidine                                | TTP                        | 21                                  |

G-CSF = granulocyte colony-stimulating factor; GM-CSF = granulocyte-macrophage colony-stimulating factor; AML = acute myeloid leukemia; MDS = myelodysplastic syndrome; TTP = thrombotic thrombocytopenic purpura

## Reporting an ADR

Many are concerned about the recent failure of the FDA to comprehensively report on serious ADRs. Even when ADRs are discovered early and are included in the drug's initial package insert, the comprehensiveness of the safety information disseminated by the FDA or pharmaceutical sponsor is frequently poor.

Oncologists can also report ADRs to independent pharmacovigilance organizations such as the Research on Adverse Drug events And Reports (RADAR) project. RADAR focuses on identify-

ing serious ADRs in the oncology setting. Between 1998 and 2007, RADAR reported 33 serious ADRs related to hematology and oncology drugs. Although the quantity of ADR reports in RADAR databases is generally smaller than in the FDA database (Table 1), the quality of these reports is often better. RADAR is led by Dr. Charles L. Bennett at Northwestern University in Chicago, IL. For more information, contact Dr. Bennett at [cbenne@northwestern.edu](mailto:cbenne@northwestern.edu).

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