Rapid Reporting and Review of an Increased Incidence of a Known Adverse Event


The National Cancer Institute (NCI) sponsors cancer clinical trials throughout the United States. Many of these trials are conducted by one of the groups of investigators that participate in the nine adult cancer cooperative groups (CCGs). CCGs typically have a single operations office and a single statistical office. Primarily, CCGs perform clinical trials to advance the treatment of cancer. In every trial, patient safety is of paramount importance. CCG investigators are required by the NCI to report some or all adverse events. An adverse event is defined by the U.S. Food and Drug Administration (FDA) as “any undesirable experience associated with the use of a medical product in a patient” (1). On the basis of the NCI Common Toxicity Criteria (2), each adverse event is graded on a 5-point severity scale: 1 = mild, 2 = moderate, 3 = severe, 4 = life-threatening, and 5 = lethal. In trials involving cytotoxic chemotherapy, radiation therapy, or both, adverse events are expected. Each CCG has procedures to monitor adverse events and to take appropriate action if the rate of adverse events is unacceptably high.

Typically, the first step in the development of new treatments is a phase I clinical trial to determine safe drug dose(s) and schedule(s). When a new treatment regimen is taken from a phase I trial to a phase II or III trial, several factors must be considered. Phase I trials often include patients with any solid tumor type (as opposed to a specific type) and are conducted at specialized cancer centers (as opposed to a community or multi-institutional setting). Patients enrolled in phase I trials are highly selected, often for their ability to tolerate prior therapy with standard cytotoxic agents and because they are clinically robust. Therefore, care must be taken in subsequent trials in patient populations different from those studied in the phase I testing.

Recognizing the need for careful patient monitoring, the NCI has formal adverse event-reporting requirements in phase II and III trials, as outlined in Table 1 (3). Each trial is reported under either “investigational” or “commercial” requirements; the more inclusive investigational requirements apply to studies that utilize agents requiring an Investigational New Drug Application to be on file with the FDA (4). Events meeting these criteria are labeled “adverse drug reactions (ADRs)” and are required to be reported in writing to the Investigational Drug Branch of the Cancer Therapy and Evaluation Program of the NCI within 10 working days of their occurrence. We will refer to this reporting process as “ADR reporting.” For perspective, during the past 3 years, approximately 75% of phase II trials conducted by the North Central Cancer Treatment Group (NCCTG) have used commercial, as opposed to investigational, reporting requirements. Adverse events not requiring ADR reporting are reported with the use of each CCG’s standard data collection procedures.

In CCG trials using commercial reporting requirements, rapid detection of an increased incidence of a known adverse event, as is required by the NCI, can be challenging, since typically few patients are enrolled at each of many locations. For example, the NCCTG has more than 200 treatment locations. Therefore, personnel at one center are unlikely to detect an increased incidence of a known adverse event. However, all adverse event data are submitted to a single statistical center that should be able to detect such an increased incidence.

For rapid detection of an increased incidence of an adverse event, entry, entry takes up to 1 month. On the basis of these timelines, detection of an increased incidence of a known adverse event, via data routinely submitted, entered, and reviewed, may not occur until months after the patient event.

In 1997, the NCCTG initiated a phase II trial evaluating a chemotherapy regimen in a relatively rare advanced disease setting. While this agent and administration schedule were FDA approved for the treatment of another disease, this NCCTG study was the first U.S. experience in the new disease setting. The agent’s primary adverse events (emesis, diarrhea, and neutropenia) were considered to be “known” or “expected” adverse events. From the period December 1997 through April 1998, five NCCTG institutions registered seven patients from five different locations. Only one membership enrolled more than one patient (three patients). Approximately 2 months after the seventh patient was enrolled, the study’s principal investigator was notified by the site enrolling the three patients that all three had been hospitalized because of diarrhea and/or neutropenia. At the same time, the principal investigator was notified by a different location that a patient had been hospitalized because of myelosuppression following treatment.

In emergency situations, NCCTG requests that each membership fax immediately all information that has not already been submitted to the statistical center. Within 24 hours of activating this emergency protocol, it was evident that four of seven patients with available data had been hospitalized for an “expected” (expected based on the package insert) event that was reported through the standard process described previously. In April 1998, these adverse events were not in the NCCTG database; therefore, the study monitoring team was not aware of their occurrence.


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On the basis of this newly available information, registration was suspended, but not before two final patients had been registered and treated. Treating physicians were notified and instructed to monitor their patients closely. However, the final two patients were both hospitalized because of treatment-related adverse reactions, and one of these two subsequently died of treatment-related complications.

Consequently, the NCCTG developed a data-collection system reporting all life-threatening or fatal adverse events and hospitalizations in a “real time” manner. The system was designed to be timely, to be user friendly, and to require no duplication of effort (i.e., if formal ADR reporting is required, no additional reporting is necessary). The reporting system is based on a form submitted to notify the statistical office of life-threatening or fatal adverse events not requiring a formal ADR (see Fig. 1). This form must be submitted to the NCCTG Statistical Center within 5 working days after a site identifies an event; database entry occurs within 24 hours of receipt. The goal is to provide information to facilitate real-time decisions regarding patient safety derived from all treatment locations.

To disseminate information rapidly, a computer program run nightly generates an e-mail report detailing all newly entered adverse events identified through this system and provides a history of adverse events reported previously. This e-mail report is sent to the study’s principal investigator, statistician, and data-monitoring assistant. This information, in conjunction with information regarding the expected and maximal allowable adverse event rates in that particular disease setting, is used by the study team to make a decision regarding possible study modification.

This system is active for virtually all NCCTG phase II and III studies and is required in all new NCCTG studies. It was also adopted by the Mayo Clinic Cancer Center (MCCC), which serves as the research base for the NCCTG. The reporting mechanism can be modified or removed from any individual protocol by the study team with proper justification.

This system has proven itself in three ongoing NCCTG/MCCC trials. In one example, an increased incidence of an expected adverse event was observed after eight patients enrolled in a phase II trial, leading to a dose reduction. In a second case, a phase II trial investigating an agent in two patient populations was modified to reduce the drug dose and subsequently to exclude further enrollment of one patient population. Each of these protocol modifications occurred rapidly and without suspension of patient accrual, thus ensuring patient safety.

Table 1. Definition of adverse drug reactions (ADRs) in cancer cooperative group clinical trials*

| Investigational agent | 1) Unknown reaction: any grade ≥2 adverse event  
| 2) Known reaction: any grade 4 or 5 adverse event |
| Commercial agent | 1) Any unexpected grade 4 or 5 adverse event  
| 2) Any increased incidence of a known ADR which has been reported in the package insert or the literature |

*Grade 1 = mild, grade 2 = moderate, grade 3 = severe, grade 4 = life-threatening, and grade 5 = fatal (2).
Clinical trial performance demands efficient, effective mechanisms to ensure patient safety. In the trial described, we identified and addressed a problem area for CCG clinical trials. We consider the resulting reporting system to be an important improvement in our standard operating procedures and one that may have broad applicability in other clinical trial environments.

**REFERENCES**


**NOTES**

This study was conducted as a collaborative effort of the North Central Cancer Treatment Group and the Mayo Clinic.

Supported in part by Public Health Service grants CA25224, CA37404, CA35269, and CA15083 from the National Cancer Institute, National Institutes of Health, Department of Health and Human Services; and by the Linse–Bock Foundation.

Manuscript received November 23, 1999; revised March 23, 2000; accepted April 12, 2000.