Challenges of Evaluating the Cardiac Effects of Anticancer Agents

Susan E. Bates,[1] Douglas R. Rosing,[2] Tito Fojo,[1] and Richard L. Piekarz[1]

"When a man is tired of London, he is tired of life; for there is in London all that life can afford." The words of English literary scholar Samuel Johnson can also be used to describe the development of new cancer therapies, an undertaking of sufficient challenge to fill a lifetime of research. This current issue of *Clinical Cancer Research* includes an article that highlights this challenge, by reporting on a series of cardiac events observed in patients with metastatic neuroendocrine tumors treated with the histone deacetylase inhibitor depsipeptide, FK228. Fifteen of a planned 16 patients were enrolled in the trial, which was closed early due to the observed events.

The report by Shah et al. (1), leads one to the conclusion that depsipeptide is frequently associated with intolerable cardiac toxicity. As some variation of the phrase "a high number of *serious* adverse events" appears eight times, one could conclude that this is the article's main message. That cardiac-related adverse events occurred is indisputable, but describing all of these as serious adverse events can be disputed. In the reported study, patients with metastatic neuroendocrine tumors were treated on a day 1, 8, and 15 schedule with a 4-hour infusion of depsipeptide. One patient with metastatic carcinoid who had completed four cycles of depsipeptide without incident died 24 hours after receiving his first dose of the fifth cycle. Because the autopsy examination did not identify a cause of death, it was concluded that the patient probably had an arrhythmic event. Subsequently, the Institutional Review Board required 24-hour telemetry following depsipeptide infusion in all patients treated on the protocol. During telemetry, two patients had grade 2, asymptomatic, self-limited bursts of ventricular tachycardia—a single 8-beat run of a wide-complex tachycardia in a 50-year-old patient and two episodes of ventricular tachycardia, 6- and 12-beat runs, respectively, in a 68-year-old male patient. No pretreatment monitoring was done in these patients. Following depsipeptide infusion, three patients had QTc intervals of 492, 495, and 499 ms; although clearly elevated, these were also scored as CTC grade 2. Based on this spectrum of cardiac events, the authors conclude that there were a high number of serious adverse events.

However, the term "serious adverse event" has a very specific definition in drug development (Table 1) and is not used to quantify the severity of a specific toxicity since these are usually quantified using the National Cancer Institute Common Terminology Criteria (CTC) for Adverse Events. The CTC provide clinical investigators with a common language for describing toxicities on clinical trials. Nonhematologic toxicities, such as cardiac toxicity, are considered to be intolerable or dose-limiting if they reach a grade 3 or higher level of severity. Dose-limiting toxicities constitute serious adverse events only if they meet the criteria set out by the Food and Drug Administration, including toxicities that are life-threatening, require inpatient hospitalization or prolongation of hospitalization (Table 1). Death is always a serious adverse event. We would argue that, in the language of clinical drug development, the term "serious adverse event" in the Shah article should be reserved for the one sudden death. The term "serious" in academic medical oncology is a specialized term that should not be applied to grade 2 toxicities.

Shah et al. considered factors other than depsipeptide that may have played a role in the cardiac events but could not identify a common cardiac risk factor, a conclusion that is probably not surprising in a patient population with heterogeneous clinical histories and concurrent medications. The patient who died unexpectedly on this study had multiple risk factors for sudden death (Table 2); including uncontrolled hypertension with severe biventricular hypertrophy, hypokalemia, and concomitant therapy with long-acting octreotide. The adverse event documentation notes that a blood pressure of 197/105 mm Hg was recorded prior to the dose of depsipeptide. Despite treatment with metoprolol and losartan/hydrochlorothiazide, we can surmise that the hypertension had been poorly controlled, based on the biventricular hypertrophy (left greater than right) seen at autopsy, with the heart weighing 640 g (normal up to 350 g for a 70-kg man). Furthermore, the patient had hypokalemia: 140 mEq potassium raised the serum potassium from 3.3 to only 3.6 mmol/L, suggesting a marked total body potassium deficit. Finally, the patient was receiving concomitant octreotide which, as noted in the report, has been associated with QT prolongation (2). Added to the 14 ms increase associated with depsipeptide (3), a cumulative effect on the QT interval may have occurred, as discussed below. Thus, this patient had several identifiable risk factors for sudden death. Whether the carcinoid syndrome itself was a risk factor, we do not know; data relevant to this in the absence of carcinoid heart disease could not be found (4).

On-study deaths are of great concern in clinical drug development—to the individual investigators, to the sponsors, and to the Food and Drug Administration. Sudden death as a serious adverse event poses special problems, and any sudden death apparently unrelated to underlying disease on a clinical trial requires scrutiny. This is especially true in clinical oncology, where the ability to anticipate death from disease offers patients that inimitable gift—the opportunity for end of

Authors' Affiliations: [1]Medical Oncology Branch, National Cancer Institute and [2]National Heart, Lung, and Blood Institute, Bethesda, Maryland
Received 4/26/06; accepted 5/4/06.
Requests for reprints: Susan E. Bates, Medical Oncology Branch, National Cancer Institute, Building 10, Room 12N226, Bethesda, MD 20892. Phone: 301-402-1357; Fax: 301-402-1608; E-mail: sebates@helix.nih.gov.

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Table 1. Serious adverse events

A serious adverse event is defined by the Code of Federal Regulations 312.32 as follows:

Any adverse drug experience occurring at any dose that results in any of the following outcomes:

- Death
- A life-threatening adverse drug experience
- Inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant disability/incapacity
- A congenital anomaly/birth defect

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse drug experience when, based on appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

NOTE: The complete regulatory description is available at: http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?FR=312.32.

life reconciliation. Furthermore, sudden death differs from other grade 5 events in that no intervention can be attempted to reduce the toxicity. Yet, some level of perspective is required. Sudden death has been described during the development of other anticancer agents. Among 472 patients enrolled in a phase II trial of doxorubicin reported in the July 1973 issue of the journal *Cancer*, four were reported as having sudden death, and two patients developed irreversible congestive heart failure (5). In addition, 43 patients (9%) were noted to have ECG changes, mostly nonspecific ST and T wave changes. Today, doxorubicin is a widely used anticancer drug and we perform careful cardiac monitoring of patients receiving doxorubicin (as well as daunorubicin or idarubicin) and often discontinue doxorubicin when the total dose exceeds 450 mg/m^2 due to the increased risk for cardiotoxicity. Similar experiences were reported early in development for paclitaxel, cisplatin, interferon, interleukin-2, and arsenic trioxide (5–12).

The findings in the neuroendocrine study should be viewed in the larger context of the National Cancer Institute–sponsored clinical development of depsipeptide. More than 500 patients have been treated on these trials, with intensive ECG monitoring incorporated into a number of the studies. With >4,000 ECGs analyzed, several effects of depsipeptide have been noted: an increase in heart rate, ST-T wave flattening and/or T wave inversion, and QTc prolongation (3). Although the effect of concomitant antiemetic therapy as a confounding or comorbid factor cannot be excluded, it is thought that these ECG changes are effects that can be attributed, at least in part, to depsipeptide. In contrast, no evidence of myocardial damage due to depsipeptide has been discerned (3). Canine data cited in the article report histopathologic evidence of cardiac damage due to the infusion of depsipeptide on a daily or biweekly basis. However, it should be noted that these cardiac findings were observed in the National Cancer Institute preclinical dose-finding studies concomitantly with many other toxicities including intestinal necrosis, pulmonary cellular infiltration and necrosis, and lymph node depletion or necrosis; and that the schedules differed from those declared suitable for clinical development (Investigator's Brochure). Current clinical data including >1,100 troponin levels obtained following drug administration convincingly show that depsipeptide does not cause myocardial damage at the doses and schedule currently administered in clinical trials (3).

Among the >500 patients treated with depsipeptide to date, five unexpected deaths have been reported in addition to the patient with metastatic neuroendocrine cancer described in the study by Shah et al. One patient with esophageal cancer and extensive visceral disease died 10 days following drug administration; symptoms of chest pain and shortness of breath, suggestive of pulmonary embolus, were reported prior to cardiorespiratory arrest. The remaining four patients were presumed to have sudden cardiac deaths (only two had autopsies). From a careful review of these cases, it has been recognized that each patient had at least one of the known risk factors for sudden death, summarized in Table 2 (13, 14). These included valvular heart disease, coronary artery disease, hypertrophic cardiomyopathy, sarcoidosis, electrolyte abnormalities, and concomitant therapy with a QTc-prolonging agent. The patient described by Shah et al. had multiple risk factors. Given that ST and T wave changes, QT prolongation, and torsades de pointes in one patient have been observed with other HDAC inhibitors, including SAHA, LAQ824, and LBH589B (15–19)—these EKG changes may represent a class effect due to HDAC inhibition. Thus, a hypothesis emerges for class-specific drug toxicity: patients with risk factors for sudden

Table 2. Risk factors for sudden death

Coronary artery disease
Ischemic cardiomyopathy
Non-ischemic cardiomyopathy
Arrhythmogenic right ventricular cardiomyopathy
Hypertrophic cardiomyopathy
Hypertension with left ventricular hypertrophy (27)
Sarcoidosis
Amyloidosis
Myocarditis
Valvular heart disease
Congenital heart disease
Cardiac tumors
Long QT syndrome
Brugada syndrome
Wolff-Parkinson-White syndrome
Electrolyte abnormalities
Thyrotoxicosis
Proarrythmia from antiarrhythmic agents
Cocaine
Certain noncardiac QTc-prolonging drugs*

NOTE: Risk factors for sudden death as defined in refs. (13, 14, 27).
*Antipsychotic drugs were associated with as much as a 6-fold increase in sudden death risk (14). Antiemetic serotonin 5-HT3 receptor antagonists such as ondansetron and palonosetron were not included in this study.

death could be at increased risk when treated with a histone deacetylase inhibitor.

The question of QTc prolongation following depsipeptide therapy was addressed in our recent report (3). The available data strongly suggest that depsipeptide (when administered concurrently with ondansetron, itself reported to prolong the QTc by 5 ms) prolongs the QT interval, with a mean of 14 ms and a range from −49 to +78 ms. Among the 2,000 ECGs evaluated in 42 patients with T cell lymphoma who had intensive electrocardiographic monitoring while on depsipeptide, 20 ECGs from 10 patients had QT intervals of >480 ms, and 6 of these 10 patients had associated hypokalemia. These QTc intervals were calculated with the Bazett formula, which overestimates the QTc interval at higher heart rates, rather than the Fridericia formula. Although it is generally felt that patients with drug-induced QT prolongation have increased risk when the interval exceeds 500 ms, this is not firmly established. The danger posed by a prolonged QT interval is uncertain; assumptions are based on experiences with patients with the congenital long QT syndrome (20). These patients have mutations in the α chain of the hERG potassium channel. Patients with levels >500 ms have an increased incidence of torsade de pointes and sudden death (2). Sudden death associated with the administration of prescription drugs may be mediated through QTc prolongation that progresses to torsade de pointes. Indeed, a recent study of 775 cases noted a 2.7-fold increased risk of sudden death associated with noncardiac agents that prolong the QT interval (14).

In recent years, significant effort has been dedicated to defining risk due to QTc prolongation for drugs in development. It is acknowledged that the level of risk is different, depending on how widely available the agent will be. For example, the antihistamine terfenadine was removed from the market with a measured QT interval increase of 6 ms (21). However, because anticancer agents have a different risk-benefit profile, it is difficult to discern what level of QT interval prolongation would be unacceptable. Except for granisetron, the serotonin 5-HT3 receptor antagonists routinely used for control of emesis in oncology are associated with a 5 ms QT interval prolongation (22, 23). The recently released ICHE14 guidance on the Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-arrhythmic Drugs (http://www.emea.eu.int), which applies to agents widely available to the population as well as anticancer agents, acknowledges that QTc intervals >500 ms are of particular concern. The guidance notes that multiple levels of analyses ought to be included in drug development, and recommends classifying increases in the QTc >30 and 60 ms as the two levels of QTc prolongation worthy of note. Whatever the precise change that is indicative of risk, it is widely understood that combining drugs that prolong the QT interval can result in more than additive QT prolongation. This has led to a strategy that avoids the concomitant use of drugs that prolong the QT interval in ongoing studies with depsipeptide, a strategy that should be considered for other agents of this class.

We would argue that the history of oncologic drug development teaches perseverance. The histone deacetylase inhibitors have documented efficacy, including durable complete responses, in patients with T cell lymphoma (15, 24, 25). Should a new and promising class of agents with a novel mechanism of action potentially exploitable for dozens of cancer types be abandoned? Defining and controlling the therapeutic index of a new oncology agent poses special challenges given the gravity of the disease outcome, its morbidity, and the effect of potential benefit (26). If we chose to discard agents with potential toxicities, we would fail to bring our patients the best possible therapies for cancer. We would also have failed to learn from investigators who saw beyond the cardiotoxicity of doxorubicin and trastuzumab, the mucosal toxicity and nephrotoxicity of methotrexate, the bladder toxicity of cyclophosphamide, the nephrotoxicity of cisplatin, and the hypersensitivity reactions to paclitaxel. Our anticancer armamentarium, still a work in progress, would be much narrower than it is today.

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