Cardiac safety biomarkers are increasingly employed in the preclinical and clinical development of investigational oncology products. Irrespective of overt clinical toxicities, cardiac-related laboratory tests can influence decision making at many levels during the conduct of clinical studies, including eligibility for protocol therapy, dose delivery or discontinuation, and analyses of optimal dose(s) for subsequent development. Given the potential for serious and irreversible morbidity from cardiac adverse events, it is understandable that cardiac safety test results have major impact on study conduct and patient management. Applications of cardiac safety tests are often extrapolated from experiences with drugs or populations, which can differ substantially from those of a new investigational oncology agent. Thus, careful considerations are needed when cardiac safety testing is applied to clinical research or patient management.

The study by Piekarz et al. (1) reported in this issue of CCR provides noteworthy examples of such careful considerations applied by investigators from the NIH. The focus of this report is to describe cardiac safety findings in 42 patients with T-cell lymphoma enrolled in a phase 2 study of the histone deacetylase inhibitor depsipeptide (FK228). Depsipeptide is one of several histone deacetylase inhibitors in development for treatment of T-cell lymphomas and solid tumors, including breast, lung, thyroid, and colon cancers. Early reports of cardiac adverse events observed after depsipeptide and other histone deacetylase inhibitors led to the comprehensive cardiac testing, designed as ancillary safety end points of a phase 2 protocol. The report also describes risk mitigation strategies employed by the investigators to limit adverse events while preserving the opportunity for access to this promising new agent. Cardiac assessments included three categories: electrocardiographic abnormalities and QT/QTc prolongation, left ventricular function, and serum markers of myocyte damage. Risk mitigation strategies included conventional rules for dose modification or discontinuation coupled with some less conventional approaches that deserve further discussion.

**Electrocardiographic Abnormalities and QT/QTc Prolongation**

Major efforts and resources are being expended to characterize the QT prolonging effects of drugs early in development, based on the recognition that drug-induced QTc prolongation can contribute to a life-threatening arrhythmia called torsades de pointes. The fundamental recommendation of the regulatory guidance, ICH E14, is that most new drugs should have an assessment of effect on cardiac repolarization by undergoing a formal evaluation in a “thorough QT/QTc (TQT) study.” The TQT study is a single, placebo-controlled trial intended to precisely quantify drug-related QTc prolongation, a protocol primarily designed from experience with healthy volunteers or subjects with nononcologic conditions. However, the performance of a TQT study remains challenging, if not impossible for many investigational oncology agents, especially for treatments, such as depsipeptide, that cannot be studied at therapeutic exposures in healthy volunteers. Moreover, patients with advanced T-cell lymphoma enrolled to this trial often have current or impending morbidities from the advanced malignancy; thus, they do not accept prolonged dosing with placebo plus a washout period as required for the formal TQT study.

In view of the major difficulties to conduct a formal TQT study for an oncology product, it is understandable that these National Cancer Institute investigators employed an alternative protocol design to characterize drug-related QTc changes. Eligibility criteria required a baseline QTc not greater than 500 milliseconds, a level consistent with grade 2 and severity criteria in the National Cancer Institute Criteria for Adverse Events v3.0 and different from the 450- to 470-millisecond criteria used in nononcology studies; nonetheless, this did not lead to adverse outcomes, and it did enable opportunity for wider access to treatment by patients with advanced lymphoma. Optimal protocol designs for QTc assessment for oncology continue to be a topic of discussion in the regulatory and research communities, efforts that could be considered a critical path to enable more efficient clinical development of promising new cancer treatments.

The authors conclude that QTc prolongation was induced by depsipeptide. Because the study design could not employ placebo treatment nor time-matched controls, this conclusion and the reported magnitude of QTc changes could be confounded by several factors, including nausea/vomiting, administration of antiemetics or other concomitant medications, electrolyte changes, or diurnal variation. Conclusions about QTc prolongation would have been strengthened by consistent administration of the same antiemetic, such as granisetron given before QTc testing, electrocardiograms during a 1-day run-in period to assess diurnal variation, and analyses of pharmacokinetic-pharmacodynamic relationships. Pharmacokinetic testing was incorporated into the protocol, but the data were not evaluated for this publication. In the context of developing other oncology agents with a concern for major QTc prolongation and arrhythmia, the conduct of this study supports some practical strategies for risk assessment and...
management, including correction of hypokalemia and hypomagnesemia, attention to concomitant medicines, use of a consistent antiemetic when required, and electrocardiogram testing timed to coincide with peak plasma levels of the experimental agent and major metabolite(s).

**Left Ventricular Function**

The evaluation of left ventricular function has traditionally been measured by serial testing with either echo or multiple gated acquisition scans to determine left ventricular ejection fraction; (LVEF), and such assessments were incorporated into the present study. The investigators’ plan to analyze LVEF, based on last follow-up, “to allow assessment of function after the patient had received the most depsipeptide possible,” likely reflects assumption of the paradigm of anthracycline-induced left ventricular dysfunction, whereby cardiac effects are cumulative and dose related. Anthracycline-related LVEF declines, measured by serial multiple gated acquisition or echo scan are commonly accepted to be cumulative and progressive and, based on this prior experience, categorical LVEF declines mandate permanent discontinuation of anthracycline treatment even in an asymptomatic patient who is experiencing control of advanced malignancy. In contrast, the emerging experience with trastuzumab suggests yet another paradigm in which declines in LVEF may be transient and not necessarily predictive of progressive cardiac damage (2). Some patients with asymptomatic LVEF declines continue to tolerate trastuzumab treatment coupled with additional monitoring of cardiac function, and similar anecdotal experience has been reported with bevacizumab (3). These observations have implications for analyses and treatment discontinuation rules employed with other oncology agents in clinical development.

**Serum Markers of Cardiac Myocyte Damage**

Serum cardiac safety biomarkers, such as troponin and B-type natriuretic peptide, are being explored in trials of anticancer agents (4). The current study illustrates dynamic changes and sensitivity of serum cardiac troponin I results especially when compared with creatine phosphokinase. However, the cardiac troponin I results were notable for lack of predictive accuracy for clinically significant myocardial damage. Without a clear causal relationship to depsipeptide, elevated cardiac troponin I was observed before protocol treatment in three patients and as a single elevation after treatment in ~15% of enrolled patients. Despite this laboratory finding, several patients continued treatment in the study without overt cardiac abnormalities during the safety follow-up period. These results support the conclusion that a single troponin elevation did not reflect major cardiac abnormalities to preclude further treatment and are consistent with observations from other published reports, indicating that cardiac biomarker elevations can be confounded by laboratory technique, comorbidities, or advanced malignancy (5). The findings also suggest that serum cardiac safety biomarkers, measured by serial testing in patients who have advanced malignancy but no other cardiac findings, may require careful consideration when applied to future oncology protocols. Moreover, Criteria for Adverse Events v3.0 criteria for severity of troponin elevation, often based on single laboratory finding without other signs or symptoms, may deserve qualification and further evaluation to gain understanding of performance characteristics for prediction of clinical morbidity.

What can be learned about the safety of depsipeptide? The extensive cardiac monitoring does support the authors’ conclusions that this agent can be given without high frequency of acute cardiac toxicities. Long-term follow-up extending beyond 3 years in some patients provides some assurance that the various laboratory abnormalities were not associated with late-onset cardiac events. Further development of this agent can build from these findings, coupled with considerations for risk management to limit cardiac morbidities.

What can be learned about risk management of other experimental agents developed in patients with advanced malignancy? The investigators provide some important experience about electrocardiograms, troponin levels, and other laboratory findings that were frequently confounded by comorbidities. Importantly, they also provide examples of cardiac laboratory findings that were successfully assessed and managed at the bedside instead of terminating treatment with the experimental agent, thus preserving the opportunity for patients to obtain durable disease control.

Clearly, cardiac liabilities should not broadly preclude development and marketing of promising new cancer treatments, and oncologists have shown their ability to manage complicated cardiac risks in clinical investigations and general practice (6). This study represents an important contribution for future clinical development of depsipeptide. Continued research is needed to assess cardiovascular safety of patients with advanced malignancy. Additionally, efforts are needed to refine strategies for risk management, avoiding unintended consequences that negatively affect patient access and clinical development of promising new cancer treatments. The report by Piekarz, et al. provides some thoughtful risk management experience generated by an organized collaboration between oncologists and cardiologists who supported this development program, and these learnings should have relevance to other oncology agents with cardiac safety concerns.

**References**

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Howard J. Fingert and Mary L. Varterasian


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