HDAC Inhibitors and Cardiac Safety

To the Editors: Shah et al. (1) reported on the cardiotoxicity of the histone deacetylase inhibitor Romidepsin (depsipeptide, FK228) administered weekly ×3 q28, in 15 patients with metastatic neuroendocrine tumors. The study was terminated early due to a high number of “serious cardiac adverse events” comprising of one sudden death, asymptomatic grade 2 ventricular tachycardia in two patients, and prolonged QTc interval in three patients all probably related to Romidepsin.

Our team has been involved in the development of several histone deacetylase inhibitors including Romidepsin, LAQ-824, PXD101, and R306465. We are in the final stages of a phase II study of Romidepsin in metastatic castration-refractory prostate cancer for which we have reported antitumor activity (2). We have not observed (a) sudden death, (b) drug-induced ventricular arrhythmia, or (c) prolonged QTc interval. We initially reported grade 1 and grade 3 QTc prolongation in one and two patients, respectively, as recorded by automated electrocardiogram readings (2). However, when the electrocardiograms of these patients were reviewed with independent manual calculation using Bazett’s correction formula, it was recognized that the presence of nonspecific asymptomatic T wave flattening had resulted in the incorrect automated description of QTc prolongation. This T wave flattening has been observed with all the histone deacetylase inhibitors studied at our center, despite the different chemical properties of these drugs suggesting a drug class effect. The only electrocardiogram changes of note observed in our phase II trial, with the same dosing schedule as Shah et al.’s study (1) were (asymptomatic) nonspecific grades 1 and 2 ST segment changes. Our findings are in line with those of Piekarz et al. (3), which were published in last month’s edition of this journal.

In a phase I study of LAQ-824 in patients with solid tumors, we reported QTc prolongation of >500 ms in one patient (4). With PXD101, one patient experienced short-lived atrial fibrillation at the maximum tolerated dose (5); however, no significant QTc prolongation was observed. ST and T wave changes, QTc prolongation, and/or torsade de pointes have been reported with SAHA, LBH589B, and MS-275 (6). Overall, these data suggest that the electrocardiogram changes were related to dose and schedule. We believe that chronic oral administration of lower drug doses may abrogate such toxicity. With such schedules, however, fatigue and nausea remain significant cumulative toxicities.

The conclusions drawn by Shah et al. (1) should not lead us to slow the development of an agent that has shown promising activity in castration-refractory prostate cancer and cutaneous T-cell lymphoma. The authors rightfully state that the population studied may have subclinical carcinoid heart disease, which may be a predisposing factor for serious cardiac events (1). Cardiac monitoring should be conducted in present and future studies, but patient selection remains key in order to minimize concurrent risk factors for cardiac events, which were clearly present for the patients described by Shah et al. (1).

References
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Rhoda Molife, Peter Fong, Michelle Scurr, et al.


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