Managing Cardiac Risk Factors in Oncology Clinical Trials

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In recent years, the development of clinical trials using targeted agents has been stimulated by the identification of pathways involved in carcinogenesis, metastasis, and drug resistance and by the emergence of molecular analysis of tumors. These targeted agents are initially investigated as single agents in phase I clinical trials, and, if well tolerated, in phase II and III studies. However, some targeted agents can cause arrhythmia, hypertension, ischemia, or left ventricular (LV) dysfunction. Because determination of the maximum tolerated dose and dose-limiting toxicity are primary endpoints of phase I clinical trials, many useful targeted agents that cause excess cardiac toxicity might not proceed to phase II trials. Therefore, cardiac risk factors should be taken into account in the selection and management of patients with cancer who are enrolled in phase I clinical trials.

Trastuzumab, a monoclonal antibody against human epidermal growth factor receptor 2 (HER2), was approved in 1998 for the treatment of early stages of HER2-positive breast cancer. The use of trastuzumab is associated with improved clinical outcomes, but it can induce a decrease in LV systolic function. Vascular endothelial growth factor (VEGF) signaling is an essential step in angiogenesis, and angiogenesis contributes to cancer progression. Anti-VEGF agents, including bevacizumab, sunitinib, and sorafenib, are approved as anticancer therapies, but their use is associated with hypertension, heart failure, and thromboembolic events. In phase I through III clinical trials, the reported incidences of grade 3–4 hypertension with bevacizumab, sunitinib, and sorafenib were 9.2%, 6.9%, and 7.2%, respectively.[1] Grade 3–4 LV systolic dysfunction was noted in 0.3%, 1.4%, and 0.05% of patients, respectively, whereas the rates of grade 3–4 thromboembolism were 9.6%, 1.2%, and 3.8%, respectively.[1] Sunitinib, especially in patients with a history of hypertension, can compromise cardiac reserves and induce heart failure.

Vascular-disrupting agents are a class of drugs that target the vasculature of solid tumors. These drugs have promising antitumor activity, but their use is associated with cardiovascular events. Phase I and II studies of the investigational agents combretastatin A1 diphosphate (CA1P), dimethyloxoxanthene acetic acid (ASA404), verubulin hydrochloride (MPC-6827), and combretastatin A4 phosphate (CA4P) reported cardiovascular events—most commonly hypertension, tachyarrhythmias and bradyarrhythmias, atrial fibrillation, and myocardial infarction. In a phase I trial of MPC-6827 in patients with advanced cancer, the dose-limiting toxicity was myocardial infarction.[2]

Anthracyclines have been extensively used as anticancer therapy, but their use is associated with dose-dependent cardiotoxicity. Non-anthracycline chemotherapeutic agents, when used in conjunction with anthracyclines, can synergize with them and lead to diastolic dysfunction and ischemia.[3] Concomitant or sequential administration of anti-HER2 agents or angiogenesis inhibitors can increase cardiotoxicity by facilitating the progression of asymptomatic diastolic dysfunction toward systolic failure or accelerated symptomatic ischemia.

Patients with cancer who are under treatment with potentially cardiotoxic drugs should be closely monitored for cardiotoxicity. Particular attention should be paid to those who have one or more of the following risk factors: obesity, hypertension, diabetes mellitus, hypercholesterolemia, or a history of smoking, cardiac disease, anthracycline therapy, or radiation therapy that included the chest. Patients treated with potentially cardiotoxic anticancer therapies should be monitored with seri-

al measurements of the LV ejection fraction, troponin I levels, and B-type natriuretic peptide. The use of troponin I monitoring has several advantages: it has an almost absolute cardiac specificity and high sensitivity, it is minimally invasive, it is less expensive than echocardiograms or multigated acquisition scans, its measurement is standardized (no interobserver variability), it has a high negative predictive value, and its functionality is independent of the underlying mechanism of cardiotoxicity.[4] In recent years, QTc prolongation has been used as a marker for screening patients for enrollment in phase I clinical trials with anticancer agents. Although QTc prolongation can predict acute cardiac arrhythmia, it does not predict LV dysfunction.

Early detection of subclinical cardiac damage and initiation of prophylactic treatment in high-risk patients can significantly abrogate the occurrence of overt clinical cardiotoxicity. Cardiotoxic agents should be discontinued in patients who develop heart failure until stabilization on appropriate therapy has been established. In most patients, cardiotoxicity is reversible upon discontinuation of the offending agents, and, after a period of stabilization, therapy can be resumed. Management of anti-VEGF-induced hypertension has been proposed.[5] Some investigators have suggested that hypertension may be a biomarker of a patient's responsiveness to anti-VEGF therapy, but this view needs to be validated in further studies.

Awareness of anticancer therapy–associated toxicity will lead to early detection and appropriate management of cardiovascular complications. Optimal management of cardiac risk factors should decrease cardiovascular complications and enable the true benefits of investigational agents to emerge.

References

1. Vaklavas C, Lenihan D, Kurzrock R, Tsimberidou AM. Antivascular endothelial growth factor therapies and cardiovascular toxicity: what are the important clinical markers to target? Oncologist 2010;15(2):130-41.
2. Tsimberidou AM, Akerley W, Schabel MC, Hong DS, Uehara C, Chhabra A, et al. Phase I clinical trial of MPC-6827 (Azixa), a microtubule destabilizing agent, in patients with advanced cancer. Mol Cancer Ther 2010;9(12):3410-19.
3. Minotti G, Salvatorelli E, Menna P. Pharmacological foundations of cardio-oncology. J Pharmacol Exp Ther 2010;334(1):2-8.
4. Cardinale D, Colombo A, Torrisi R, Sandri MT, Civelli M, Salvatici M, et al. Trastuzumab-induced cardiotoxicity: clinical and prognostic implications of troponin I evaluation. J Clin Oncol 2010;28(25):3910-16.
5. Mouhayar E, Salahudeen A. Hypertension in cancer patients. Tex Heart Inst J 2011;38(3):263-5.