REVIEW ARTICLE

Cardiovascular Toxicity and Management of Targeted Cancer Therapy

John B. Bossaer, PharmD, Stephen A. Geraci, MD and Kanishka Chakraborty, MD

ABSTRACT

The advent of effective oral, molecular-targeted drugs in oncology has changed many incurable malignancies such as chronic myeloid leukemia into chronic diseases similar to coronary artery disease and diabetes mellitus. Oral agents including monoclonal antibodies, kinase inhibitors and hormone receptor blockers offer patients with cancer incremental improvements in both overall survival and quality of life. As it is imperative to recognize and manage side effects of platelet inhibitors, beta blockers, statins, human immunodeficiency virus drugs and fluoroquinolones by all healthcare providers, the same holds true for these newer targeted therapies; patients may present to their generalist or other subspecialist with drug-related symptoms. Cardiovascular adverse events are among the most frequent, and potentially serious, health issues in outpatient clinics, and among the most frequent side effects of targeted chemotherapy. Data support improved patient outcomes and satisfaction when primary care and other providers are cognizant of chemotherapy side effects, allowing for earlier intervention and reduction in morbidity and healthcare costs. With the implementation of accountable care and pay for performance, improved communication between generalists and subspecialists is essential to deliver cost-effective patient care.

Key Indexing Terms: Cancer therapy; Oral therapy; Outcomes; Toxicities and side effects. **[Am J Med Sci 2016;351 (5):535–543.]**

INTRODUCTION

Productive research has identified many oral cytotoxic and targeted agents to treat cancer. Until the late 1990s, cancer drugs were limited to chemotherapy agents, with the exception of receptor blockade for hormonally responsive tumors and all-trans retinoic acid for acute promyelocytic leukemia (APL). With the advent of imatinib, erlotinib and trastuzumab, the era of molecular-targeted therapy began. Oral topotecan, chlorambucil and 5-fluorouracil (5-FU) were available 20 years ago, but their use in a limited subspecialty patient population did not overlap with the internist's practice. Currently, the efficacy and success of oral antihormonal agents in breast and prostate cancer, Food and Drug Administration (FDA) approval of imatinib for chronic myeloid leukemia (CML), capecitabine (5-FU prodrug) use in multiple malignancies and the availability of erlotinib (and other multikinase inhibitors) as palliative treatment options for visceral malignancies has transformed oncologic care.

This shift of focus to molecularly targeted agents created incremental improvements in care but at the cost of diverse side effects, creating adverse event management challenges (Figure 1). Increased survival, functional status and opportunities for side effects have greatly increased the need for all healthcare providers to practice with heightened awareness of drug-induced disease in their patients with cancer. Cardiovascular toxicities are frequently encountered and can cause irreversible morbidity or death. This review focuses on the cardiovascular side effect profiles of commonly prescribed targeted agents and, where available, management options (Figure 2). Information from the oncologist on prognosis and potential treatment side effects can help the primary care provider to better share responsibility for care of patients with cancer.[1]

HYPERTENSION

Vascular endothelial growth factor (VEGF) is a molecular target for antineoplastics (including multikinase inhibitors) that inhibit angiogenesis.[2,3] The incidence of hypertension is 20-30% with bevacizumab, and 15-60% with VEGF-targeting tyrosine kinase inhibitors (TKIs).[4,5] Bevacizumab-induced hypertension appears to be mediated by both a decrease in capillary and arteriolar density (capillary rarefaction) and a suppressed nitric oxide activity.[6,7] Sunitinib has similar effects.[8] Bortezomib and thalidomide can also cause orthostatic hypotension due to autonomic dysfunction.[9]

There are no conclusive data supporting any preferred treatment of hypertension secondary to antiangiogenic drugs. Experientially, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, beta blockers and non–dihydropyridine calcium-channel blockers all appear effective.[10] A treatment algorithm, consistent with American Heart Association guidelines, is provided (Figure 3).[11] Inhibitors of CYP 3A4 (e.g., diltiazem and verapamil) should be avoided with TKIs,

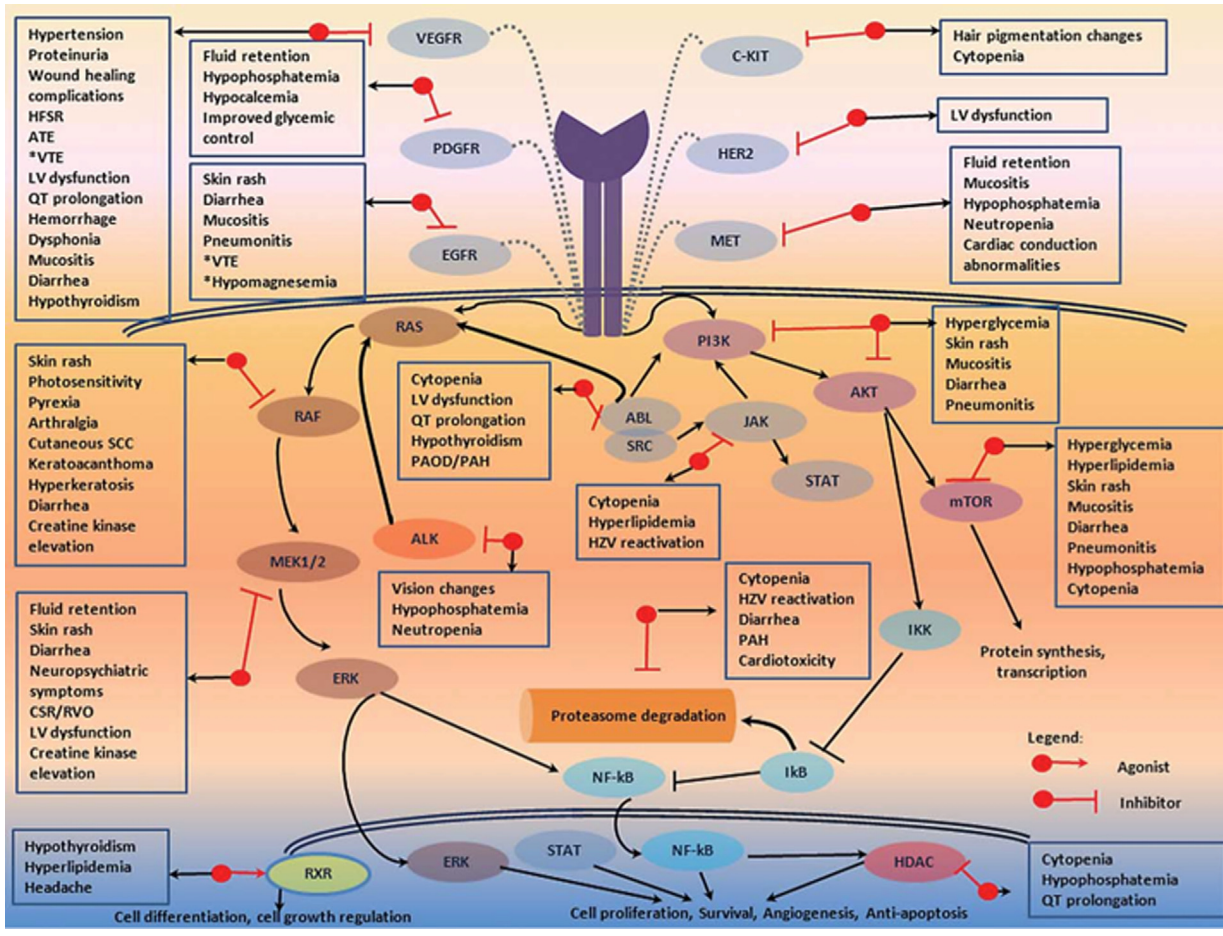

FIGURE 1. Targets and associated toxicities of newer cancer therapies. ATE, arterial thromboembolism; CSR, central serous retinopathy; HZV, herpes zoster virus; LV, left ventricular; PAH, pulmonary arterial hypertension; PAOD, progressive arterial occlusive disease; RVO, retinal vein occlusion; SSC, squamous cell cancer; VTE, venous thromboembolism. (Reprinted with permission from Dy GK.[2])

because most are substrates of this cytochrome.[4,12,13] The selection of an antihypertensive regimen should be collaborative between the generalist and oncologist. It is also important to continue a balanced approach to manage chronic underlying cardiovascular risk factors (diabetes, dyslipidemia, smoking, obesity and inactivity) for optimal management of drug-induced hypertension or cardiomyopathies.[14,15] The reader is referred to focused reviews recently published on VEGF-induced hypertension for additional insight.[16,17]

CARDIOMYOPATHY

Generalists are likely aware of the cumulative, dose-dependent risk of left ventricular (LV) systolic dysfunction from anthracyclines. Several targeted agents also increase this risk, most notably inhibitors of human epidermal growth factor receptor-2 (HER2), imatinib, trametinib and several TKIs used for treating renal cell carcinoma (RCC).

HER2-Targeted Therapies

Antineoplastic agents targeting HER2 can cause a dilated cardiomyopathy that is generally reversible with drug discontinuation. Trastuzumab treatment resulted in asymptomatic reductions in left ventricular ejection fraction (LVEF) in 7.5%, and frank congestive heart failure in 1.9%, of patients across 10 clinical trials.[18] The risk of trastuzumab-induced cardiomyopathy is much higher when it is coadministered with anthracyclines (relative risk = 5.43: 95% CI: 1.93-15.29; $P = 0.01$).[18] Ado-trastuzumab emtansine combines a microtubule inhibitor with trastuzumab to not only inhibit HER2 but also preferentially deliver chemotherapy to cells overexpressing HER2. Ado-trastuzumab emtansine caused a decrease in LVEF (to <0.50, or 15% below baseline) in 1.7% of treated patients in 1 report.[15]

Pertuzumab, also a HER2-targeting monoclonal antibody, binds to a different epitope of HER2 than trastuzumab and is used in combination with trastuzumab. Surprisingly, it was incidentally noted that dual HER2 therapy with