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THE PRESENT AND FUTURE

STATE-OF-THE-ART REVIEW

Vascular and Metabolic Implications of Novel Targeted Cancer Therapies

Focus on Kinase Inhibitors

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ABSTRACT

Novel targeted cancer therapies, especially kinase inhibitors, have revolutionized the treatment of many cancers and have dramatically improved the survival of several types of malignancies. Because kinases not only are important in cancer development and progression, but also play a critical role in the cardiovascular (CV) system and metabolic homeostasis, important CV and metabolic sequelae have been associated with several types of kinase inhibitors. This paper reviews the incidences and highlights potential mechanisms of vascular and metabolic perturbations associated with 3 classes of commonly used kinase inhibitors that target the vascular endothelial growth factor signaling pathway, the ABL kinase, and the phosphoinositide 3-kinase/AKT/mammalian target of rapamycin signaling pathway. We propose preventive, screening, monitoring, and management strategies for CV care of patients treated with these novel agents.
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The past decade has been marked by a revolution in cancer therapy with the development of novel targeted therapies that have improved the prognosis of many cancer types. This progress has resulted, in part, from a new paradigm for cancer treatment with an evolution from relatively nonspecific cytotoxic agents to more selective, mechanism-based therapeutics. Unfortunately, adverse short- and long-term cardiovascular (CV) toxicities are important considerations with some of the novel therapies, prompting development of the new clinical field of cardio-oncology (also referred to as "onco-cardiology"). Although there has been much focus on the cardiomyopathic effects of cancer therapies, adverse vascular and metabolic sequelae of the novel cancer therapies have emerged as an important issue.

Tyrosine and serine/threonine kinases are important targets for cancer therapy, and these kinase inhibitors have become the fastest growing class of anticancer drugs (1). In general, kinase inhibitors are less toxic than older cancer therapies such as anthracyclines, alkylating agents, or ionizing radiation because they target cellular pathways that have been hijacked by the cancer cell. However, as kinases also play critical roles in the CV system, kinase inhibition can have adverse CV effects (2). Toxicities may be *on-target* where the intended target kinase

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also plays a critical role in CV system. In this case, such on-target toxicities may even serve as surrogates for antitumor response (3). On the other hand, most kinase inhibitors also inhibit kinases other than the cancer-promoting target, resulting in *off-target* toxicities.

Because many of the new kinase inhibitors target the vasculature or cancer metabolism, vascular and metabolic derangements have emerged as important issues in cardio-oncology. Moreover, multiple tyrosine kinase inhibitors (TKIs) are known to cause thyroid dysfunction, which can potentially complicate metabolic derangements (4). Coupled with the heterogeneity of both *on-* and *off-target* effects of specific agents, a wide spectrum of CV toxicities have been associated with these kinase inhibitors. This review will focus on the vascular and metabolic toxicities associated with 3 categories of kinase inhibitors commonly used in cancer therapy, categorized on the basis of their cellular targets: 1) kinase inhibitors targeting the vascular endothelial growth factor signaling pathway (VSP); 2) kinase inhibitors targeting ABL kinase; and 3) kinase inhibitors targeting the phosphoinositide 3-kinases (PI3Ks)/AKT/mammalian target of rapamycin (mTOR) signaling pathway.

KINASES AS TARGETS FOR CANCER THERAPY

Kinases are enzymes that transfer ≥1 phosphate group from adenosine triphosphate (ATP) to specific protein or lipid substrates. Kinase-directed modifications of these substrates control cell signaling, which regulates diverse cellular functions. Dysregulation of kinases can lead to a variety of pathologies, including malignancy. Indeed, most human cancers are associated with overactivation of kinases due to somatic point mutations, chromosomal rearrangements, or gene amplifications. There are approximately 20 lipid kinases and 518 protein kinases encoded by the human genome. On the basis of their substrate specificity, protein kinases can be further categorized into tyrosine kinases (TKs), serine/threonine kinases, and dual-specificity kinases. TKs are the most important targets for cancer drug development. For this reason, the majority of kinase inhibitors currently approved or in clinical trials are TKIs (5).

TKs can be classified as receptor tyrosine kinases (RTKs) and nonreceptor TKs. RTKs span the plasma membrane and are activated by binding of a ligand (most commonly a growth factor) to the extracellular domain, leading to dimerization of the receptor and activation of signaling. In contrast, nonreceptor TKs are located in the cytosol, the nucleus, or the inner surface of the plasma membrane and play an important role in relaying intracellular signals triggered by RTKs and other cell-surface receptors (**Central Illustration**) (6). To activate a substrate, kinases bind both the substrate and ATP, then transfer a phosphate group from ATP to the substrate, leading to substrate phosphorylation and activation.

Strategies to target kinases in cancer therapy include (**Central Illustration**):

1. Small molecule kinase inhibitors (TKIs): small molecules (molecular weight <1,000 Daltons) that interfere with binding of the kinase to ATP or substrates. Most current drugs targeting kinases belong to this category.
2. Monoclonal antibodies (mAbs) that bind the RTK or its ligand. As a result, they can be further subcategorized into mAbs directed against RTKs to prevent ligand binding (e.g., trastuzumab) or RTK dimerization and activation (e.g., pertuzumab); and mAbs directed against the circulating ligand to prevent it from binding to its receptor (e.g., bevacizumab).
3. Soluble decoy receptors ("ligand traps") bind the ligand, preventing it from binding to its receptor.

Small molecule inhibitors have been especially attractive for clinical use because they can be taken orally and can target more than 1 kinase, thus proving effective in several types of cancer.

CV ENDPOINTS IN ONCOLOGY TRIALS VERSUS CV TRIALS

As life expectancy increases, many diseases that predominantly affect older individuals will become more prevalent. Advancing age is a risk factor for CV disease, metabolic disorder, and cancer. Importantly, cancer and CV disease also share other common risk factors, such as tobacco use, obesity, and physical inactivity (7). As a result, cancer patients frequently have CV and metabolic comorbidities. Therefore, in the assessment of new cancer therapies, it becomes essential to distinguish between treatment-induced CV and metabolic adverse effects from treatment-independent events. A robust and consistent monitoring system with standard definitions for treatment-associated CV and metabolic adverse events is essential during the treatment course. In addition, to definitively determine whether a therapy causes CV disease, appropriate control groups are prerequisites.

ABBREVIATIONS AND ACRONYMS

BP = blood pressure

CTCAE = Common Terminology Criteria for Adverse Events

CV = cardiovascular

mTOR = mammalian target of rapamycin

PI3K = phosphoinositide 3-kinase

RTK = receptor tyrosine kinase

TKI = tyrosine kinase inhibitor

VEGF = vascular endothelial growth factor

VSP = vascular endothelial growth factor signaling pathway