REVIEW ARTICLE

Personalized Oncology in Interventional Radiology

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ABSTRACT

As personalized medicine becomes more applicable to oncologic practice, image-guided biopsies will be integral for enabling predictive and pharmacodynamic molecular pathology. Interventional radiology has a key role in defining patient-specific management. Advances in diagnostic techniques, genomics, and proteomics enable a window into subcellular mechanisms driving hyperproliferation, metastatic capabilities, and tumor angiogenesis. A new era of personalized medicine has evolved whereby clinical decisions are adjusted according to a patient's molecular profile. Several mutations and key markers already have been introduced into standard oncologic practice. A broader understanding of personalized oncology will help interventionalists play a greater role in therapy selection and discovery.

ABBREVIATIONS

ATP = adenosine triphosphate, ALK = analplastic lymphoma factor, BCR-ABL = breakpoint cluster region/the Abelson tyrosine, BRAF = v-raf murine sarcoma viral oncogene, CD-20 = clusters of differentiation-20 (antigen of B-cells), c-KIT = tyrosine-protein kinase kit or mast/stem cell growth factor receptor, CML = chronic myelogenous leukemia, CRC = colorectal carcinoma, EGFR = epidermal growth factor receptor, EML4 = echinoderm microtubule-associated protein-like 4, FDA = Food and Drug Administration, HCC = hepatocellular carcinoma, HER-2 = human epidermal growth factor receptor-2, KRAS = Kirsten rat sarcoma viral oncogene, mAb = monoclonal antibody, mTOR = mammalian target of rapamycin, NSCLC = non–small cell lung carcinoma, PDGFR = platelet-derived growth factor receptor, SMKI = small molecule kinase inhibitor, VEGF = vascular endothelial growth factor, VEGFR2 = vascular endothelial growth factor receptor-2

The incidence of cancer and deaths from cancer is projected to increase globally (1). Although there have been major advances in both understanding of cancer biology and technologic achievements in diagnosis and treatment (1,2), this knowledge has been translated only slowly and incrementally into successful therapies or outcomes. Traditional chemotherapeutic drugs were aimed nonspecifically at cell division processes; however, newer targeted drugs have been engineered selectively for specific cellular pathways and processes (proteins, genes, organs, or stromal cells) important for tumor growth (1). Many of these so-called targeted therapies employ unique characteristics of the cancer cells to inhibit them more efficiently, and these therapies may improve survival (1,3). In the late 1990s, a new era of personalized oncology began with the approval of the anti–human epidermal growth factor receptor-2 (HER-2)–targeted monoclonal antibody (mAb) agent trastuzumab in the treatment of breast cancer (4). A companion diagnostic test for HER-2 was subsequently approved. Over the last 2 decades, numerous new tests and anticancer agents based on biomarker profiles have been investigated (3,4). Imatinib treatment for gastrointestinal stromal tumor or chronic myelogenous leukemia was another early successful drug to be specifically engineered and designed for a very specific target. Targeted drugs have since become standard therapies in a range of malignancies, including liver cancer, breast cancer, lung cancer, lymphoma, and melanoma. Despite certain successes, however, the full potential for targeted therapies on overall cancer mortality has yet to be realized (1,3,5). This article defines the basic concepts, reviews the current status of major targeted therapies affecting personalized oncology, and defines the vital role played by the interventional radiologist.

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CONCEPTS

The Cancer Genome Atlas project was launched in 2006 by the National Institutes of Health to explore genetic variance specific to individual cancers (6). Key in this process has been the identification of unanticipated driver mutations in some cancers. Mutations are 100-fold to 500-fold more frequent in cancer cells compared with normal cells (7). The genomes of cancer cells within a tumor are extremely variable both temporally and spatially, across histologies as well as within specific tumors. This variability has led to distinction between driver or causal and passenger mutations (2,5,7). Driver mutations actively drive the neoplastic process conferring increased growth rate or the ability to invade surrounding tissues and metastasize. Passenger mutations do not initially contribute to the disease process but may become important in the context of resistance or other mutations (2,5,7). Identification of causal mutations would help stratify patients' risk, prognosis, and the likelihood of response but is complex because increased background mutations in cancer cells decreasing the "signal-to-noise ratio" (3,5,8). Identifying subcellular mechanisms and developing effective therapies is challenging (8). The ideal targeted therapy would focus on a unique characteristic of subcellular mechanisms specific to the neoplastic process, enabling a selective destruction of tumor cells without nonspecific toxicity (1,3).

An array of new terminology has emerged, such as "pharmacogenomics" (9), the influence of genetic variance on drug response, and "theragnostics or theranosis" (10), combining diagnostic and therapeutic interventions to predict responses and determine patient selection (2,7). The goal of personalized medicine is to apply data mining to the large amounts of data collected about individuals to enable prediction of potential disease, prevention by improved surveillance and assessment of high-risk groups, and personalized care according to a patient's profile with active participation from patients in the decision-making process (7). Personalized medicine is based on the "4 P's": predictive, preventive, personalized, and participatory (2,7). Although all treatments in medicine are in theory "personalized," cancer has become the focus for a more selective and rationally engineered personalization process. The ability to apply personalized therapy to date has been made possible through key partnerships such as with interventional radiology (IR). Investigators engaging IR colleagues early during protocol development can optimize the timing, placement, and use of specialized tissue acquisition through this multidisciplinary collaboration.

Interventional radiologists need to be appraised of these concepts to contribute in a significant manner. In this article, general concepts pertaining to biomarkers, subcellular pathways, and targeted therapies are initially outlined. Then specific biomarkers and targeted therapies approved by the U.S. Food and Drug Administration (FDA) are discussed for solid tumors most frequently encountered in IR practice. Finally, the role of IR is reviewed.

BIOMARKERS

The two major categories of biomarkers informing the process of a patient's care are prognostic and predictive biomarkers (11). There is a plethora of prognostic biomarkers—biomarkers that provide information about potential outcome, such as survival or metastatic potential. More important to success of personalized therapeutic direction is development and validation of predictive biomarkers—biomarkers that inform potential to respond to an intervention. Critical to the success of targeted therapy application, validated predictive biomarkers are currently few in number and generally require tissue for discovery and validation, sometimes in the form of paired tissue sampling. Validated predictive biomarkers may also have prognostic potential (12,13).

Some predictive biomarkers are the targets of drugs involved in molecular pathways, DNA repair, or polymorphisms in genes involved in drug metabolism (2,12). For example, patients with colorectal carcinoma carrying UGT1A1*28 polymorphism showed higher risk of hematologic toxicity compared with patients who were not carriers, although this was only for the first treatment cycle. More importantly, these patients also showed a higher response rate to chemotherapy (14). Such biomarkers may be used to predict response to therapy and determine optimal or patient-specific drug cocktails (13). Prognostic biomarkers predict the natural course of disease, such as molecules involved in angiogenesis, dedifferentiation, and invasiveness (12,13). Genetic variability of vascular endothelial growth factor (VEGF) receptors has been linked with differing therapeutic responses and toxicity. For example, patients with breast cancer and VEGF-2578AA genotype showed increased overall median survival with bevacizumab and paclitaxel versus paclitaxel alone compared with patients with other VEGF genotypes (15). Prognostic biomarkers are biomarkers that describe outcome differences independently of therapeutic intervention. For example, before the introduction of HER-2–targeted therapy, amplification of HER-2 was a negative prognostic sign in breast cancer, associated with worse overall survival and response to all therapy compared with tumors without HER-2 amplification.

MAJOR PATHWAYS

Protein products of mutated genes interact with one another and define a biochemical or developmental pathway that confers growth or antiapoptotic advantages to cells (8). Several pathways exist, and an exhaustive list is beyond the scope of this article, but epidermal growth factor receptor (EGFR) activation plays a major role in cell proliferation and growth in several solid tumors.