Science and Mechanism of Action of Targeted Therapies in Cancer Treatment

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Objectives: *To identify common signaling pathways that control cancer growth and discuss the mechanism of action of cancer targeted therapies.*

Data Sources: *Medical and nursing literature, research articles, published clinical guidelines.*

Conclusion: *Understanding the signaling pathways and genetic mutations that control cancer cell growth elucidates an understanding of the mechanism of targeted therapies.*

Implications for Nursing Practice: *To understand the mechanism of action of targeted therapies, oncology nurses must first be familiar with the most common signaling pathways. Adding to this foundation, the nurse can easily learn about the classes of targeted therapies and the strategies to minimize and manage common side effects.*

Key Words: *Signaling pathways, targeted therapy, monoclonal antibodies, tyrosine kinase inhibitors*

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In the past half century, the treatment of cancer has evolved from a single, highly toxic, chemotherapeutic drug such as nitrogen mustard, to targeted therapies that disrupt specific signaling pathways and are more easily tolerated than traditional anti-cancer drugs. In between, cancer treatments have included combinations of drugs, combinations of modalities such as concurrent chemotherapy and radiation or sequential neoadjuvant chemotherapy, surgery, then adjuvant chemotherapy, and finally biotherapy and immunotherapy.

Targeted therapies are designed to attack a specific target in the cell that subsequently interferes with a growth pathway. Advances in molecular biology and genomic sequencing technology have led to the identification of many therapeutic targets within cancer cells and the design of treatments to interfere with them. These new therapies have fewer and less toxic side effects because they act with precision on specific targets in the growth pathways with little collateral damage to healthy cells and tissue. This article provides an overview of signaling pathways that influence the growth of cancer cells and the mechanism of action of the common targeted therapies used in cancer treatment.

Mechanisms of Action

The growth, death, and differentiation of normal and cancer cells alike are controlled by the action of signaling molecules and pathways. Normal cells are protected with safeguards that are altered in cancer cells. Cancer cells are characterized by uncontrolled growth, absence of apoptosis (programmed cell death), increased blood vessel formation, and local invasion into surrounding tissue or distant metastases.

The normal cell processes are activated when an extracellular ligand (growth factor) binds to a receptor on the cell surface. The activation, called *dimerization*, sends a signal across the cell membrane to the intracellular domain where tyrosine kinase activation occurs. Like the ripple effect of a pebble tossed in the pond, this activating signal causes a cascade of intracellular signaling that may go as far as the DNA in the nucleus. The signals can either promote cell division or cause cells to stop growing; the balance of the two types of signals determines the rate of cell growth.

Signal transduction pathways are the mechanisms by which extracellular activation signals are carried into the cell's cytoplasm and nucleus. The proteins involved are growth factors, growth factor receptors, signal transduction proteins, cell-cycle control proteins, and DNA repair proteins.[1] Kinases are proteins that perform phosphorylation, that is, carry phosphates from one stop in the signaling pathway to the next.[2] Upstream signaling events occur near the cell membrane and those occurring closer to the nucleus are considered to be downstream.[3]

Cancer cells often make more growth factor receptors than normal cells. This overexpression allows continuous activation of signaling pathways. Other cancer cells have genetic mutations that allow dysfunctional receptors to remain in the "on" position for growth, even in the absence of the growth factor.[2] Other ways that normal signaling processes are bypassed occur when there are increased levels of proteins in the pathways or if genetic mutations alter the proteins in the pathway. Altered proteins may then transmit signals on their own to promote growth or interfere with the signals that should tell the cell to stop growing.

A number of growth-promoting proteins and signaling pathways have been identified and are being studied in cancer laboratories and in clinical trials. These proteins are activated by gene amplification or genetic alterations, such as point mutations or driver mutations, that cause continuous activation of signaling.[4] Examples of these growth promoting proteins are KRAS, EGFR, BRAF, MEKo-1, HER-2, MET, ALK, and RET.[5] The clinical significance of studying these genetic mutations is realized in the actionable genes identified in non–small cell lung cancer (NSCLC) and melanoma tumors. The identification of the presence of these mutations and gene rearrangements in these two diseases now directs standard of care treatments.[6]

Targeted therapies are designed to interfere with dysfunctional signaling of cells to stop the growth of cancer cells.[2] Specifically, the growth factor receptors can be blocked or turned off, receptors can be blocked from interacting with other receptors, and signals can be blocked inside the cell. Targeted therapies interfere with the signaling pathways by both extracellular and intracellular events. Binding of the ligand (growth factor) and receptor overexpression resulting in receptor activation are extracellular processes. Intracellular pathways that activate signaling include binding of intracellular proteins, cross talk, receptor mutations, and loss of regulatory mechanisms.[7]

Signaling Pathways

To understand the mechanism of action of targeted therapies, oncology nurses must first be familiar with the most common signaling pathways (Fig. 1).[7] Adding to this foundation, the nurse can easily learn about the classes of targeted therapies and the strategies to minimize and manage common side effects. Table 1 lists the type and