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Tyrosine Kinase: Targeted Anti-Cancer Therapy

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Cancer chemotherapy focused towards large molecules or enzymes fails to differentiate between normal and cancerous cells, ultimately leading to numerous lethal adverse effects. Erratic, incomplete and short-term tumor responses have been observed from cytotoxic chemotherapies. In contrast, tumor development or progression is halted by targeted therapies by interfering with the molecular targets. These targeted therapies will provide greater specificity toward cancerous cells along with wider therapeutic window and low toxicity. These therapies are in combination with conventional chemotherapy provides additive or synergistic anti-cancer activity. Hence, targeted therapies may provide beneficial clinical effects ultimately leading to a novel and encouraging approach to chemotherapy. Out of several targeted therapies, tyrosine kinase inhibitors are being explored as leading cancer therapy [1,2]. Tyrosine kinases act as an important mediator in the modulation of growth signaling cascade. They play a critical role in numerous biological developments such as differentiation, metabolism and apoptosis with respect to external and internal stimuli. Recent advances have shown their vital role in pathophysiology of cancer. Although, their activity is strongly regulated in non-cancerous cells, they may secure altering functions due to mutations, overexpression and autocrine paracrine stimulation, leading to malignancy. Small molecule tyrosine kinase inhibitors are considered as promising therapeutic approach because of their selective blocking tactic towards constitutive oncogenic activation in tumor cells [1,3].

Enzymes responsible for catalyzing the transfer of the γ phosphate group from adenosine triphosphate to target proteins are referred as tyrosine kinases [2,4]. They are categorized as (i) receptor tyrosine kinases (RTK) such as epidermal growth factor receptor (EGFR/ErbR), platelet-derived growth factor receptor (PDGFR), vascular endothelial growth factor receptor (VEGFR) and fibroblast growth factor receptor (FGFR); and (ii) non-receptor tyrosine kinase (NRTK) such as SRC, ABL, FAK and Janus kinase. Receptor tyrosine kinase also possesses enzymatic kinase activity in addition to being cellular surface membrane receptors. The RTK has a multi-domain extracellular ligand for assigning ligand specificity, a single pass transmembrane hydrophobic helix and a cytoplasmic portion holding a tyrosine kinase domain. The structural organization of NRTK has a kinase domain and frequently owns several additional signaling or protein-protein interacting domains [3,5-7].

Tyrosine kinases play a vital role in cancer molecular pathogenesis. They have been also recognized as potential anticancer targets leading to number of marketed anti-cancer drugs. Sequencing efforts by Human genome project has efficiently utilized tyrosine kinases and thus provided more opportunities in the filed on anti-cancer drug discovery. Current advances in the field of molecular pathophysiology of cancer have provided vast information about tyrosine kinases. RTK have been found to be upstream or downstream of epidemiologically relevant oncogenes or tumor suppressors. Tyrosine kinase inhibitors are utilized to target RTK which is overexpressed in cancer have been recognized as a potential target using [3,5,8-18]. In the past decade, the US Food and Drug Administration have approved several tyrosine kinase inhibitors which have been listed in Table 1.

Tyrosine Kinase Inhibitor	Target	Class
Afatinib	EGFR/ErbB2	Small Molecule
Axitinib	VEGFR1/VEGFR2/ VEGFR3/PDGFRB/c-KIT	Small Molecule
Bosutinib	BcrAbl /SRC	Small Molecule
Cetuximab	ErbB1	Monoclonal Antibody
Crizotinib	ALK/Met	Small Molecule
Dasatinib	Multiple Targets	Small Molecule
Erlotinib	ErbB1	Small Molecule
Fostamatinib	Syk	Small Molecule
Gefitinib	EGFR	Small Molecule
Ibrutinib	BTK	Small Molecule
Imatinib	Bcr-Abl	Small Molecule
Lapatinib	ErbB1/ErbB2	Small Molecule
Nilotinib	Bcr-Abl	Small Molecule
Pazopanib	VEGFR2/PDGFR/c-kit	Small Molecule
Pegaptinib	VEGF	RNA Aptamer
Ruxolitinib	JAK	Small Molecule
Sorafenib	Multiple Targets	Small Molecule
Sunitinib	Multiple Targets	Small Molecule
Vandetanib	Multiple Targets	Small Molecule
Vemurafenib	BRAF	Small Molecule

Table 1: List of FDA approved tyrosine kinase inhibitors [9-18].

In conclusion, the important role of tyrosine kinases in controlling cellular growth and differentiation has a profound effect in human oncologic diseases. Potential clinical applications of tyrosine kinase inhibitors have been shown by the recent approval of them for various neoplastic diseases. In addition to marketed approved tyrosine kinase inhibitors, numerous human trials are undergoing in order to bring best from them. Focus in high throughput genome based molecular therapeutics can yield tyrosine kinase inhibitors that more therapeutically effective and efficient. All these intensive effort may overlay the foundation to shape personalized cancer therapeutics.

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