OVERVIEW OF KINASE INHIBITORS AS CANCER THERAPIES

There are about 500 kinases identified in the human genome that range from minimally studied to very well characterized drug targets[1]. Kinases are broadly classified based on the substrates that include carbohydrates, lipids and proteins. Protein kinases are the largest group and can be further classified based on the amino acid residues that are phosphorylated (serine/threonine or tyrosine). Since kinases are involved in critical signaling cascades including cell proliferation, and metabolism, they are involved in disease development across multiple areas including cancer, autoimmune disease, neuronal disease, inflammation, metabolic disorders etc. About 25-33% of drug development programs target kinases[2] and these programs have resulted in the successful development and approval of 79 drugs targeting kinases[3]. The first kinase inhibitor (imatinib) was approved in 2001 for the treatment of chronic myelogenous leukemia (CML) that carry the BCR-Abl gene rearrangement[4]. A majority of the approved kinase inhibitors are used to treat different tumor types, especially hematological cancers that can be quickly diagnosed and are amenable to easy drug administration. However, as more potent inhibitors were developed for use in humans, a pattern emerged where the kinase inhibitor therapies seemed to be most efficacious in early-stage disease and did not work very well in late stage or metastatic disease[4]. Kinase inhibitor drug development typically has multiple generations where the first-generation therapy is developed and approved for a targeted patient population with a specific mutation. The next-generation of therapies are rapidly developed to be more potent and potentially target broader patient populations for a given tumor type or even target other tumor types.

One of the most important characteristics of kinase inhibitors are their promiscuity which can be a positive or negative attribute. Kinases tend to be conserved around the catalytic domain so it is very common for a given inhibitor to target multiple kinases. The positive aspect of this is that a single inhibitor can be used to treat multiple cancer types with different mutations or rearrangements. One example of the positive polypharmacology is crizotinib that was developed as a Met kinase inhibitor for non-small cell lung cancer (NSCLC) but was found to have activity against the ROS/ALK gene fusion that is a NSCLC disease driver[5]. However, one of the big issues with kinase drug development are off-targets caused by an inhibitor binding to multiple kinases that can result in unacceptable toxicity.

One specific application of kinase drug development is the inhibition of angiogenesis. The scientific hypothesis is that inhibiting the development of vasculature in a solid tumor, nutrients and oxygen supply will be cut off resulting in tumor cell death. The VEGF receptor family has been extensively targeted and one specific therapy, bevacizumab, has had significant clinical success[4]. Nevertheless, kinase inhibitors targeting angiogenesis have had challenges due to cross-reactivity with other kinases.

In recent years, the success of immune checkpoint inhibitors such as pembrolizumab have occupied the limelight for novel cancer therapies but the development of kinase inhibitors has been progressing in the background. The continued development of kinase inhibitors was highlighted by the approval of a first in class Akt inhibitor capivasertib in November 2023[6]. Capivasertib has been approved for use along with fulvestrant, an estrogen receptor antagonist, for hormone receptor positive/HER2-negative breast cancers with known PI3K/Akt/PTEN mutations[6]. Since the drug is approved for a specific breast cancer population, the FDA also approved a companion diagnostic test (FoundationOne®CDx assay)[6]. Clinical trial data showed that the combination of capivasertib and fulvestrant reduce disease progression by 50% compared to fulvestrant alone[7]. The approval of capivasertib is a landmark achievement for Akt related drug development programs as other therapies such as ipatasertib failed to achieve clinical success in castration-resistant prostate cancer and triple-negative breast cancer[7].

References:

[1] https://www.ncbi.nlm.nih.gov/pmc/articles/PMC10586788/
[2] https://www.sciencedirect.com/science/article/pii/S1043661822004984
[3] https://www.ncbi.nlm.nih.gov/pmc/articles/PMC10530957/
[4] https://www.nature.com/articles/s41573-021-00195-4
[5] https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9771320/
[6] https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-capivasertib-fulvestrant-breast-cancer
[7] https://pharmaphorum.com/news/az-first-akt-finish-line-fda-clears-narrow-label