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A FOCUS ON SELPERCATINIB'S ROLE IN PRECISION ONCOLOGY

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ABSTRACT

The drugs selpercatinib used for the target therapy for thyroid cancer when other options have been exhausted. In this discussion, we delve into the action mechanism of selpercatinib, exploring its pharmacokinetics, pharmacodynamics, and the array of side effects associated with its use. The information presented is based on a thorough review of research papers and reputable drug databases, including Drug Bank and NIV24.

INTRODUCTION

Thyroid cancer is one of the rare types of cancer which affects the thyroid gland. One of the most common symptoms in patients is a painless lump or swelling developed in the neck. Thyroid cancer accounts for about 1% of most of the cancer cases in UK. Whilst in India, as per the data published by National Centre Registry Programme, 1 in around 752 males and 1 in about 285 females will develop thyroid cancer in their lifetime.

Types of thyroid cancer

1) Papillary carcinoma

It is one of the most common types of thyroid cancer and accounts for about 60% of cases. People under the age of 40 years, particularly women, may contract this type of thyroid carcinoma.

2) Follicular carcinoma

It is not as common as papillary carcinoma but accounts for around 15% of the total cases of thyroid cancer. It usually affects older aged people

3) Medullary thyroid carcinoma

This type of cancer accounts for about 5-8% of total cases, but unlike the other types of thyroid carcinoma, it runs in families.

4) Anaplastic thyroid carcinoma

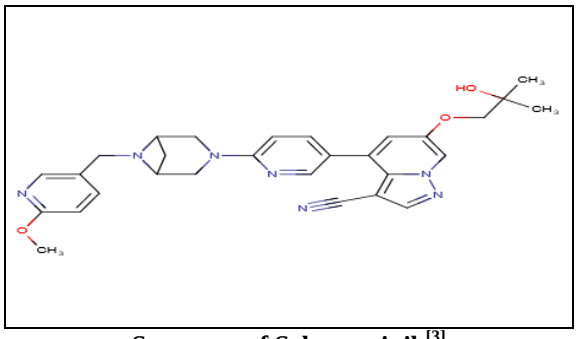
This type of thyroid cancer is one of the rarest and aggressive type and accounts for less than 5% of the total thyroid cancer cases arising. It usually affects people over the age of 60 years.

This article contains information based on the targeted therapy for thyroid cancer. Various drugs such as Levatinib (lenurima), Sorafenib (Nexavar), Carbozantinib (Cabometyx) and selpercatinib(Retevmo) are some of the drugs that can be used for the above-mentioned purposes. These drugs are mostly taken orally in form of capsules or tablets.

In this article, we will be discussing about the drug Selpercatinib (Retevmo) in detail. This drug is also known as RET inhibitor and helps to treat cancer by blocking about the genes that abnormally trigger RET gene or block the activity RET kinases. Selpercatinib has comparatively less and milder side effects than the other mentioned drugs for targeted therapy.[1,2]

DRUG INFORMATION

Selpercatinib is a drug which inhibits kinase and has high particularity for RET tyrosine kinase receptor (RTKs) than any other RTK classes. It was granted accelerated FDA approval on 8th of May, 2020. It is marketed by the brand name RETEVMO™ by Loxo Oncology Inc.[3]



Structure of Selpercatinib[3]

Table 1: Properties of Selpercatinib.[3]

Chemical formula	$C_{29}H_{31}N_7O_3$
Molecular weight	525.63 g/mol
State	Solid
Solubility in water	0.0299mg/mL
Acid dissociation constant	14.59
Base dissociation constant	6.28
Polar surface area	112.04 $Å^2$
Class of medication	Kinase inhibitor

Table 2: Formulation of selpercatinib.[3]

Dosage	Route	Strength
Tablet (coated)	Oral	160mg (for above 50 years old)
Tablet (coated)	Oral	120 mg
Capsule	Oral	80 mg

EVOLUTION OF TARGETED THERAPIES OF THYROID CANCER

Patient's when diagnosed with thyroid carcinoma, it was found that around 94% to 96% of patient's had tumor which was denoted as differentiated carcinoma which originates from the follicular epithelium. The other 2% to 3% of patients have medullary thyroid carcinoma, which originates from neuroendocrine C cells and the rest 1% patient had dedifferentiated malignancy, anaplastic thyroid carcinoma, these 1% group of patients had high percentage of fatalities.

In the 20th century treatment for thyroid carcinoma was based on surgery, for primary carcinoma surgical resection (that is removal of cancer tissues) was performed, for differentiated carcinoma thyroid lobectomy and for metastatic differentiated carcinoma radioactive iodine which is a molecularly targeted treatment(used since 1940) is used. The first person who was cured from metastatic cancer was a middle aged man and this occurred by providing 4 doses of radioactive iodine which was drunken by the man, but this radioactive iodine is only a curative intervention.

The first person to be cured from metastatic cancer was a middle-aged man, and this happened by the provision of 4 doses of radioactive iodine which was drunk by the man. However, this radioactive iodine is just a curative intervention.

In recent time, the treatment for metastatic thyroid carcinoma does not differ much from what was used 25 years ago. TSH-suppressive thyroid hormone and cytotoxic chemotherapy, such as doxorubicin, are prescribed to the patients at the symptomatic stage. When the clinical trials were done there was only a minimal changes for oncologist to succeed in any technique for treatment due to less no of patient as volunteer, some experiment were done without the acknowledgement of the patients too. Then concept of key driver oncogenes was enlighten which activated the kinases that cause carcinoma. The first mutated kinases that was targeted for inhibition were in RET gene. In the early phase 1 trail the anti-angiogenic multi kinase inhibitor(aaMKI), motesanib diphosphate inhibited RET kinase making is available for treatment for RET driven cancer. In 2004 phase two trial of motesanib was conducted for differentiated and medullary thyroid carcinoma patients. In this trial 184 patients were present in which the differentiated carcinoma patients showed a partial response rate of 14 % and 63 % showed a stable disease, that is no growth of cancer was observed. After this phase the oncologist decided that aaMKI can be used as a treatment for disease stabilization.

Back in 2013, during a phase three trail, a drug called sorafenib had been found effective and was first of its kind to be approved by the FDA. The median Progression-free survival (PFS) rate was 10.8 months when treated with sorafenib, which was 5.8 months in the placebo cohort. In another drug, vandetanib had a median PFS of 30.5 months in the vandetanib arm. But none of these drugs approved for advanced thyroid carcinoma showed improvement in overall survival. Tumour genotyping in the four aaMKI phase three trails where performed and it was noticed that in vandetanib and cabozantinib trials targeting the RET kinase could improve outcome. Patients with RET M918T showed a significant improvement in the median PFS of 13.9 months and another drug selpercatinib in recent years have shown an PFS of 18.4 months which has enhanced the overall survival by 2 years which is a greater achievement.

Knowing the biology of the disease has led to the development of an ideal treatment for the targeted therapy of thyroid carcinoma in the last 15 years, and more target-activated kinases are researched these days in hopes of improving the overall survival rate, like targeting the PAX8/PPARy fusion protein that could result in the intervention of the thyroid tumour, and many more such targeted therapeutics are being carried out.[4,5,6,7,8]

EVALUATION OF SELPERCATINIB

Mechanism of action

Rearranged during transfection (RET) represents a transmembrane receptor with tyrosine kinase properties that consists of extracellular, transmembrane and intracellular domains. Its catalytic activity is certainly needed for development of the kidney and nervous system. RET is typically activated by chromosomal alterations resulting in 5' fusions of dimerizable domains to the 3' RET tyrosine kinase domain such as KIF5B-RET and CCDC6-RET, which will lead to dimerization (joining of similar bonds to form dimers) and autophosphorylation. Constitutively activated RET causes increased downstream signalling associated with tumor invasion, migration and proliferation.

Selpercatinib, a selective RET kinase inhibitor, has shown IC_{50}(measure of drug efficiency) values between 0.92 - 67.8 nM depending on specific RET genotype.

The data provided from natural or induced resistance mutations, along with molecular modelling, suggests Selpercatinib directly inhibits RET autophosphorylation by competing with ATP for binding. Various single amino acid mutations at position 810 can inhibit Selpercatinib binding without greatly reducing the binding of ATP, and may lead to failure of treatment in some patients.

Selpercatinib inhibits other tyrosine kinase receptor family members such as VEGFR1, VEGFR3, FGFR1, FGFR2 and FGFR3, at clinically relevant dosage.[3,9]

Absorption

In a study involving patients diagnosed with locally advanced or metastatic solid tumours who were treated with selpercatinib 160 mg twice a day, the steady-state following this therapeutic regimen was reached approximately 7 days following the last dose administration. The steady-state pharmacokinetics values were as follows Cmax 2980 (CV 53%) and AUC0-24h 51,600 (CV 58%). The absolute bioavailability ranges from 60 to 82% (mean 73%) and median tmax was 2 hours after dosing. There was no apparent effect of food on the AUC or Cmax of selpercatinib. Patients who had a baseline hepatic impairment, showed a concomitant increase in AUC0-INF with mild (7%), moderate (32%), and severe (77%) hepatic impairment.[3,9]

Metabolism

Liver is the organ where selpercatinib is primarily metabolized by CYP3A4.[3,9]

Pharmacokinetics

The graph of area under the concentration-time curve and maximum clearance of selpercatinib, were assessed with dose escalations from 20-240 mg twice daily. Steady levels were attained at an average of 7 days after initiation at all the sequential increment levels from 20-240 mg. The median accumulation ratio was 3.4 when taking capsules of 160 mg twice a day orally.

Selpercatinib is mainly hepatically metabolized via the cytochrome p450 family 3A4 enzyme mechanism, and the mean bioavailability reported in several studies is 73%. No difference in bioavailability was seen with the ingestion of selpercatinib with a high-fat meal versus normal meal. The volume of distribution was about 191 L and had an apparent clearance of 6 L/h; both volume of distribution and clearance increased with an increase in body weight.

In the healthy volunteers, following a single oral radiolabeled dose of 160 mg twice a day is administered to the patient, a significant portion of the drug remained unchanged, 69% was recovered in faeces, and 24% of radioactivity was present in the urine.[10]

Pharmacodynamics

Selpercatinib exerts an anti-tumour activity in certain cancers by inhibiting mutated forms of RET tyrosine kinases. Selpercatinib may have an improved safety parameters compared to other multi-kinase inhibitors given its enhanced specificity for RET versus other tyrosine kinases. However the selpercatinib is associated with side effects like hepatotoxicity (Chemical driven liver damage), hypertension (high bllod pressure), QT interval prolongation (abnormal heart rhythms), hemorrhagic events (bleeding from blood vessel), risk of impaired wound healing, and embryo-fetal toxicity are associated with treatment by selpercatinib. Some patients may be hypersensitive to it.[3,7]

Half-life

Selpercatinib has a half-life of 32 hours in healthy individuals.[3]

Clearance

Selpercatinib has an evident clearance of 6L/h; more the body weight more is the clearance.[3]

DISCUSSION

Looking at the statistics of thyroid cancer patient (586,000 worldwide) in 2020, there is a need for treatment/medication which can increase the overall survival rate even if the cancer is metastasized as in follicular and medullary thyroid cancer the survival rate falls to 40 to 60% when metastasized, hence we need to discover effective targeted therapies like selpercatinib which inhibits RET tyrosine kinase and works as MKIs (multikinase inhibitors).

CONCLUSION

Thyroid cancer has glimpsed evolution in targeted therapies, certainly with introduction of Selpercatinib, a selective RET kinase inhibitor. By closely targeting these kinases, selpercatinib not only minimizes off-target effects but also maximizes therapeutic impact on the cancer cells themselves. This advanced treatment has shown enhanced potency and guardianship when compared to traditional therapeutic treatment, which has less specific mechanism of action. Molecular profiling advancements have identified various genetic alterations associated with thyroid cancer, paving the research towards the progress of additional targeted therapies.

REFERENCES

1. NHS 24: Thyroid Cancer
2. Dabholkar, Jyoti1,2,3; Thankappan, Krishnakumar4,5; Vaidya, Abhishek6,7. Chapter 1: Introduction to Indian Thyroid Cancer Guidelines. Journal of Head & Neck Physicians and Surgeons, 12(Suppl 1): S5-S6, January 2024. | DOI: 10.4103/jhnps.jhnps_15_24
3. Drugbank: Targeted Therapy for thyroid cancer, Selpercatinib.
4. Subbiah V, Yang D, Velcheti V, Drilon A, Meric-Bernstam F. State-of-the-Art Strategies for Targeting

RET-Dependent Cancers. Journal of Clinical Oncology: Official Journal of the American Society of Clinical Oncology, 2020 Apr; 38(11): 1209-1221. DOI: 10.1200/jco.19.02551. PMID: 32083997; PMCID: PMC7145587.

5. National Library of Medicine: Evolution of targeted therapies for thyroid carcinoma.
6. Kato S, Subbiah V, Marchlik E, Elkin SK, Carter JL, Kurzrock R. RET Aberrations in diverse cancers: next-generation sequencing of 4,871 patients. Clin Cancer Res., 2017; 23: 1988–97.
7. Wirth LJ, Cabanillas ME, Sherman E, et al. Clinical activity of LOXO-292, a highly selective RET inhibitor, in patients with RET-altered thyroid cancers. Thyroid., 2018; 28: A–171.
8. Drilon A, Hu ZI, Lai GGY, Tan DSW. Targeting RET-driven cancers: lessons from evolving preclinical and clinical landscapes. Nat Rev Clin Oncol., 2018; 15: 151–67.
9. FDA Approved Drug Products: Retevmo (selpercatinib) capsules.
10. Raj, Priyadarshini Eashwar; Bhaskar, Rekabtala; Anne, Srikanth. Selpercatinib: A narrative drug review. Cancer Research, Statistics, and Treatment, Jan–Mar 2024; 7(1): 82-90. | DOI: 10.4103/crst.crst_389_23