Selumetinib—A Comprehensive Review of the New FDA-Approved Drug for Neurofibromatosis

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Introduction

Selumetinib is a drug that inhibits the mitogen-activated protein kinase (MAPK) pathway. This pathway has a role in different cellular functions, e.g., growth regulation, cell division, and differentiation.[1] Mutations in any of the genes involved in this pathway can cause various genetic disorders that manifest as a variety of clinical features, such as developmental delays, facial abnormalities, heart defects, and tumors. These disorders are known as RASopathies. Selumetinib selectively inhibits MAPK/ERK (extracellular signal regulated kinase) kinase (MEK) enzyme, which is a kinase upstream of ERK in this pathway.[2] Due to this property, the drug has emerged as a promising therapeutic agent for various conditions caused due to defects in this pathway, such as plexiform neurofibromas (PNs) associated with neurofibromatosis type 1 (NF-1), melanoma, non-small cell lung cancers (NSCLCs), etc. Therefore, it is being investigated as a potential treatment for RASopathies. Clinical trials have shown promising clinical results in patients with certain RASopathies, such as NF-1 and Noonan syndrome.[3,4] In April 2020, the US FDA approved it as a treatment modality for symptomatic PNs related to NF-1 in pediatric patients aged ≥2 years.[5]

Mechanism of Action

Selumetinib inhibits MAPK 1 and 2, the regulating enzymes in the MAPK signaling pathway (RAS-RAF-MEK-ERK pathway).[6] This pathway helps in regulating cellular functions like growth, differentiation, proliferation, and survival.[7] RAS protein acts as a molecular switch in this pathway, which in its inactivated state is bound to GDP (guanosine diphosphate) and forms a complex with guanine nucleotide dissociation inhibitor (GDI) that prevents it from interacting with downstream effectors.[8] It is activated by the extracellular ligand–receptor binding on its cell surface. The activation of the RAS protein leads to a conformational change that enables it to bind and hydrolyze GTP (guanosine triphosphate). Once activated, RAS protein interacts with RAF kinase to initiate downstream signaling cascades. Activation of RAS is a crucial step in the RAS-RAF-MAP-ERK pathway, and any error in regulation of this pathway due to mutations in RAS or its regulators can lead to various diseases, including cancers and RASopathies.[9]

For example, in NF-1, RAS protein activation is dysregulated because of the mutation in the *NF1* gene. This gene encodes the protein neurofibromin.[10] Neurofibromin is a GTPase-activating protein and it causes activated RAS (bound to GTP) to switch to an inactive state (bound to GDP). This prevents the further activation of downstream transcription factors in the signaling pathway. The *NF1* gene mutation causes a loss or reduction in the activity of neurofibromin, which results in uninterrupted prolonged activation of RAS. The sustained activation of RAS keeps the downstream signaling pathway in a prolonged activated state, which can result in the development of various clinical manifestations of the disorder, including neurofibromas (benign tumors of the nervous system), café-au-lait spots (pigmented skin lesions), and learning disabilities.[11] Aberrant activation of this pathway is frequently seen in disorders like NSCLC, melanoma, and cancer of the

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pancreas.[12] Selumetinib has emerged as a targeted therapy for these cancers, both as monotherapy and in combination with other drugs.[13]

Selumetinib works by preventing the activation of the MEK enzyme, which further prevents downstream target activation in the pathway, including ERK, thereby inhibiting the cancer cells' proliferation and survival. In addition, it also induces the arrest of the G1 cell cycle. It also has a role in the apoptosis of cancer cells, which has been shown both *in vitro* and *in vivo*.[14] This inhibition causes the suppressed proliferation, angiogenesis, and metastasis of cancer cells.[15]

Pharmacology

Selumetinib is administered orally, usually in the form of tablets or capsules.[16] The recommended dose varies depending on the indication and patient characteristics. It is usually administered twice daily in a dose of 25 mg/m^2/dose.[17] It has a rapid oral absorption, and the peak plasma levels are attained within 1–2 h.[18] As its absorption can be affected significantly by food, it is generally given on an empty stomach.[19,20] High-fat meals have been shown to decrease the mean Cmax and AUC (area under the curve) of the drug, whereas the Tmax is increased.[21] Metabolism of selumetinib is primarily carried out by the liver.[22] The enzymes involved are CYP3A4, CYP2C19, CYP1A2, CYP2E1, CYP3A5, and uridine diphosphate glucuronosyl transferase (UGT) enzymes.[20] While CYP3A4 mainly metabolizes the drug, CYP2C19 and CYP1A2 enzymes produce N-desmethyl selumetinib, which is an active metabolite. N-desmethyl selumetinib is eliminated from the body using the same pathways as selumetinib.[20] Although it only makes up for less than 10% of plasma selumetinib levels, N-desmethyl selumetinib is more powerful, and is responsible for approximately 20% to 35% of the total pharmacological effect. The elimination t1/2 is 5–7 h and excretion is predominately through the feces.[18] The pharmacokinetics may be affected by hepatic impairment. In clinical studies, the exposure (i.e., the amount of drug in the bloodstream) of selumetinib was increased in patients with mild liver impairment. However, the increase in exposure was not clinically significant, and hence no dose adjustments were recommended for mild liver impairment. However, dose adjustments are necessary in moderate impairment, while the recommended dose for severe liver impairment has not been defined yet.[20]

The relationship between renal impairment and pharmacokinetics of selumetinib has not been extensively studied. However, renal elimination of selumetinib and its metabolites is considered to be a minor pathway of elimination, and therefore, it is unlikely that renal impairment would have a significant effect on the drug's exposure.[20]

Clinical Uses

1. **Neurofibromatosis type 1:** NF-1 affects around 1 out of 3000 people across the globe.[23,24] It is an autosomal dominant condition that causes benign tumors of the nervous system and skin. As discussed earlier, NF-1 is caused by *NF1* gene mutation, which encodes for neurofibromin. Loss of function of neurofibromin causes the failure of regulation of the MAPK pathway, resulting in the occurrence of tumors.

   PNs are benign tumors arising from peripheral nerve sheaths. These tumors usually occur as a manifestation of NF-1. PNs are most commonly observed in children, and the likelihood of developing these tumors increases with age. PNs are most commonly observed on the head, trunk, and extremities, although any part of the body can be involved.[25] These tumors grow along the nerve sheaths and can infiltrate the surrounding tissues, making surgical removal challenging. PNs can also cause a range of medical issues, depending on their location and size, such as cosmetic disfigurement, pain, compression of vital organs, and functional impairment. Studies have shown that PNs can also transform into malignant peripheral nerve sheath tumors in almost 10% of patients.[26-28]

   The mechanism of action of selumetinib in NF-1-associated PNs is similar to that of cancer, i.e., inhibition of MEK1/2, the upstream kinases that activate ERK1/2, which is an effector in the RAS-MAPK pathway. Inhibition of MEK1/2 by selumetinib leads to interference in the RAS-MAPK pathway activation, which contributes to reduced tumor growth in NF-1-associated PNs.

   Selumetinib has been evaluated in multiple trials to treat NF-1-associated PNs. In a phase II trial in children with NF-1-associated PNs, selumetinib showed a significant decrease in tumor volume as compared to placebo. The median reduction in tumor volume was 27.9% for selumetinib compared to 0.0% for placebo. Selumetinib was also associated with a reduction in pain, improvement in function, and quality of life.[29]

   In another trial in the adult population with NF-1-associated PNs, selumetinib demonstrated a significant decrease in tumor volume in comparison with baseline, with a median change of −22%. Selumetinib was also associated with a decrease in pain and improvement in function.[30] In April 2020, US FDA approved it for treating NF1-associated PNs in pediatric patients.
2. **Non-small cell lung cancer:** In NSCLC, selumetinib has a modest but significant benefit when combined with docetaxel. This combination showed a significantly higher progression-free survival (PFS) of 5.3 months in contrast to only-docetaxel therapy (2.1 months) in the KRAS-mutant variant of NSCLC, which was statistically significant.[31] However, overall survival (OS) was

similar in both the groups. Selumetinib and erlotinib were also evaluated as a combination for the treatment of *KRAS* mutant NSCLC. However, the combination therapy did not demonstrate any increase in PFS or OS than only-erlotinib therapy.[32] The most common adverse effects of selumetinib in these trials were rash, diarrhea, and nausea.

3. **Uveal melanoma:** A combination of selumetinib and dacarbazine chemotherapy was given in a phase III trial to look for potential benefits in uveal melanoma. However, the combination did not show any significant improvement in PFS (although tolerability profile was better with combination therapy).[33]
4. **Advanced melanoma:** Selumetinib was also evaluated in a phase II trial in advanced melanoma with *BRAF V600E* mutation. In this trial, a combination of selumetinib with docetaxel demonstrated a 6-month PFS of 40%, compared to 26% with chemotherapy alone. However, the OS was similar. The response rate was also better with the combination when compared to chemotherapy alone (32% vs. 14%).[34] The most common adverse effects of selumetinib in this trial were found to be rash, diarrhea, and peripheral edema. In patients with advanced melanoma, selumetinib was evaluated in combination with dacarbazine as well. This combination showed a higher PFS (5.6 months) as compared to only dacarbazine (3 months).[35] The commonest adverse effects in this trial were nausea, fatigue, and rash.
5. **Pancreatic cancer:** Selumetinib has been compared with capecitabine for the patients in whom the therapy with gemcitabine for advanced pancreatic cancer has failed. In this multicentric phase 2 trial, the median survival was 5.4 months vs. 5 months with selumetinib and capecitabine, respectively. However, the OS was almost similar in both the drugs.[36]
6. **Thyroid cancer:** In a phase II trial for radioiodine-refractory progressive papillary thyroid carcinoma, selumetinib was evaluated in combination with radioactive iodine (RAI) therapy. The combination showed a significant improvement in complete response (CR) rate compared to RAI therapy alone. It concluded that selumetinib reverses the radioiodine resistance of refractory thyroid cancer.[37] The common adverse effects of selumetinib in this trial were diarrhoea, rash, and fatigue.

FDA Approval

The first drug to be approved for the treatment of PNs is selumetinib. It was a significant milestone in the field of targeted therapies for rare diseases. On April 12, 2021, the US FDA gave approval for its use in children with NF1 and symptomatic PNs which are inoperable. The approval was given on the basis of the results of the SPRINT trial, in which 50 children were enrolled. In this phase II trial, these children were given 25 mg/m^2 selumetinib orally twice daily till the halt of disease progression.[38] The drug was stopped immediately in cases of unacceptable adverse events. Overall response rate (ORR) was considered as the primary endpoint, which included the patients showing a response to the drug (partial or complete). Duration of response (DOR), progression-free survival, and safety were considered as other endpoints. The ORR was 68%, with 18 patients (36%) showing a partial response and 16 (32%) achieving a complete response. The DOR could not be calculated, as 82% of responders were still showing a response at 12 months (by the end of the analysis). The median PFS was 22.8 months (11.0–34.7 months). The common adverse events were diarrhea, nausea, vomiting, pain abdomen, xerosis, fatigue, muscle pain, fever, acne, stomatitis, paronychia, and headache.[38]

More studies are required to assess the efficacy and safety of selumetinib in the pediatric population and to investigate its potential use in other cancers that are driven by dysregulation of the MAPK pathway.

Adverse Effects

Selumetinib has been generally well tolerated in clinical trials. The commonest adverse events were diarrhea, nausea, fatigue, skin lesions, and peripheral edema. Grade 3 or 4 adverse effects were less common and included neutropenia, anemia, and hypertension.[39,40] One of the potential risks due to inhibition of the RAS-MAPK pathway is the development of skin toxicity, including rash and acneiform lesions.[29,41] More severe adverse effects such as pneumonitis, cardiomyopathy, and retinal vein occlusion have also been reported, albeit rarely. These adverse effects can be managed with dose reductions, temporary discontinuation, or supportive care. The adverse effects of selumetinib in NF-1-associated PNs are generally similar to those observed in cancer trials. The commonest of these were rash, diarrhea, nausea, and peripheral edema. Grade 3 or 4 adverse effects were less common and included hypertension and neutropenia.[20]

Conclusion

Selumetinib has been an effective targeted therapy for several types of cancer, including advanced melanoma, NSCLC, and differentiated thyroid cancer, as well as NF-1. It blocks the MEK enzyme, the key mediator of the RAS/RAF/MEK/ERK pathway. There has been a significant increase in PFS, partial response, and complete response with this drug when compared to chemotherapy, RAI therapy, and placebo in several clinical trials. However, selumetinib has not consistently demonstrated a significant increase in OS compared to other treatments in these trials. Also, selumetinib is a safer drug to use with a few adverse effects such as skin rash, vomiting, and diarrhea. It has shown good results in the treatment of NF-1-associated PNs, with significant reductions in tumor volume and pain, resulting in better function and quality of life. It has

been approved by the FDA in children ≥2 years who have neurofibromatosis type 1-associated PNs. Selumetinib has been generally well tolerated in these patients. However, the adverse effects should be closely monitored and managed accordingly. The choice of treatment for every individual patient depends on several parameters, such as cancer stage, type and specific molecular alterations, the patient's preferences, and the availability of treatments. In some cases, combination therapy with different targeted agents or chemotherapy may show a better response in comparison with single-agent therapy. Clinical trials are going on to assess the safety and efficacy of selumetinib as a combination therapy with other agents in various cancer types.

To conclude, selumetinib is a promising targeted therapy for treating many types of cancer and NF-1. Selumetinib has shown significant improvements in PFS, response rate, and CR rate, when compared to chemotherapy, RAI therapy, and placebo in several clinical trials, but may be less effective in some indications compared to other targeted therapies. However, further studies are required to explore its uses and limitations in the context of a multidisciplinary approach to the management of different cancer types.

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Conflicts of interest

There are no conflicts of interest.

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