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Tyrosine Kinase Inhibitors in Neuroendocrine Tumors: A Concise Review

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Abstract

Neuroendocrine tumors (NETs) originate from neuroendocrine cells, which exhibit characteristics of both neurons and hormone-producing endocrine cells.Tyrosine kinase inhibitors (TKIs) are a class of medications that block the action of tyrosine kinases, enzymes responsible for cell growth and division. In some neuroendocrine tumors (NETs), these pathways are dysregulated, leading to uncontrolled tumor growth. TKIs have shown promise in treating certain NETs, particularly those that are advanced or have metastasized

INTRODUCTION

Neuroendocrine tumors (NETs) are a complex group of neoplasms originating from neuroendocrine cells, specialized cells dispersed throughout the body that possess characteristics of both nerve cells and hormone-producing endocrine cells. These tumors can develop in diverse anatomical locations, with the most common primary sites being the lungs, gastrointestinal tract (including the stomach, small intestine, appendix, colon, and rectum), and pancreas. Less frequently, NETs can arise in other organs such as the thymus, thyroid, parathyroid glands, adrenal glands, and ovaries. The diverse origins of NETs contribute to the wide range of clinical presentations and behaviors observed in patients.

While NETs are often characterized by slow growth and indolent behavior, some can exhibit aggressive growth patterns, including local invasion of surrounding tissues and distant metastasis to other organs, such as the liver, lymph nodes, and bones. This variability in tumor behavior underscores the importance of accurate diagnosis and appropriate management strategies. The slow growth of many NETs can make early detection challenging, as symptoms may be subtle or nonspecific for extended periods. Symptoms can vary depending on the location of the tumor and the specific hormones or peptides it produces. The diagnosis of NETs typically involves a combination of imaging studies, such as CT scans, MRI, and endoscopic procedures, along with laboratory tests to measure hormone levels and identify specific tumor markers(1).

Tyrosine kinase inhibitors (TKIs) are a class of medications that block the action of tyrosine kinases, enzymes responsible for cell growth and division. In some neuroendocrine tumors (NETs), these pathways are dysregulated, leading to uncontrolled tumor growth. TKIs have shown promise in treating certain NETs, particularly those that are advanced or have metastasized. Further research is ongoing to determine the optimal use of TKIs in NET management(2).

MOLECULAR PATHOGENESIS OF NEUROENDOCRINE TUMORS

Neuroendocrine tumors (NETs) originate from neuroendocrine cells, which exhibit characteristics of bo-

th neurons and hormone-producing endocrine cells. These tumors can occur in various locations throughout the body, most frequently in the lungs, gastrointestinal tract, and pancreas. The molecular pathogenesis of NETs is complex and heterogeneous, encompassing multiple genetic and epigenetic alterations(2,3).

Several key molecular pathways are implicated in NET development. Mutations in genes within the mTOR pathway, such as MEN1, PTEN, and TSC1/2, are frequently observed. These mutations can result in dysregulated cell growth and proliferation. Additionally, alterations in chromatin remodeling genes, including ATRX and DAXX, are prevalent in pancreatic NETs. These mutations can disrupt DNA repair mechanisms, contributing to genomic instability. Other genetic alterations, including mutations in TP53 and RB1, have also been identified in some NETs.

Epigenetic modifications, including DNA methylation and histone modifications, also contribute to NET pathogenesis. These modifications can alter gene expression without affecting the underlying DNA sequence. For instance, hypermethylation of tumor suppressor genes can silence their expression and promote tumor development.

The specific molecular alterations driving NET development can vary based on tumor location and other factors. Further research is necessary to fully elucidate the complex interplay of genetic and epigenetic factors in NET pathogenesis. This understanding will be essential for developing more effective targeted therapies for these tumors(1,3).

TARGETTING BRAF V600E

BRAF mutations in neuroendocrine tumors (NETs) are relatively infrequent compared to other cancers like melanoma. However, they have been reported in a subset of NETs, particularly in pancreatic and small intestinal NETs. The most common BRAF mutation observed is the V600E mutation. The presence of a BRAF mutation can have implications for treatment, as targeted therapies against BRAF V600E, such as vemurafenib and dabrafenib, may be considered. Further research is needed to fully understand the prevalence and clinical significance of BRAF mutations in different NET subtypes(4).

Dabrafenib and trametinib are recommended in combination for Neuroendocrine tumors which are BRAF V600E mutation positive.

Dabrafenib, a targeted therapy primarily employed in BRAF V600E-mutant melanoma, is currently being investigated for its potential role in treating neuroendocrine tumors (NETs). Although BRAF mutations occur in NETs, their prevalence is lower than in melanoma. Research efforts are underway to ascertain the efficacy of dabrafenib and other BRAF inhibitors in the treatment of BRAF-mutant NETs(5).

Ueberrothet al. (19) reported a case of a patient with grade 3 metastatic pancreatic neuroendocrine tumor (pancNET) with a BRAF V600E mutation. The patient received dabrafenib/trametinib (D/T) therapy.The patient showed an ongoing partial response to D/T therapy for nearly 15 months. Minimal side effects were observed during the treatment.The study suggests D/T therapy as a novel first-line option for BRAF-mutated metastatic pancNETs.Tumor testing for actionable mutations is recommended at diagnosis or progression.The patient initially received capecitabine/temozolomide (CapeTem), but the disease progressed. Molecular testing revealed a BRAF V600E mutation, leading to the selection of BRAF/MEK inhibition.The response to D/T was significant, with tumor regression at multiple sites.The authors advocated for routine molecular testing of pancNETs to identify potential treatment options.

Trametinib, a MEK inhibitor known for its role in regulating cell growth and proliferation, is currently

being investigated as a potential treatment option for neuroendocrine tumors (NETs). These tumors, originating from cells within the neuroendocrine system, present a diverse range of clinical behaviors and arise in various locations throughout the body. Given the complexity and heterogeneity of NETs, researchers are exploring the efficacy of trametinib, particularly its potential to target specific molecular pathways driving the growth of these tumors. A significant focus of ongoing research involves evaluating the effectiveness of trametinib in combination with other therapeutic agents, such as other targeted therapies or conventional chemotherapy. These combination strategies aim to enhance treatment responses by addressing multiple signaling pathways involved in NET development and progression(6).

Researchers are also concentrating their efforts on specific NET subtypes, recognizing that the genetic and molecular profiles of these tumors can influence their responsiveness to different treatments. For instance, certain NET subtypes harbor specific genetic mutations that may make them particularly susceptible to the effects of MEK inhibition by trametinib.

Preclinical studies and early clinical trials have provided promising preliminary data suggesting that trametinib may offer clinical benefit in some NET patients. However, further research, including larger-scale clinical trials with well-defined patient populations and standardized treatment protocols, is essential to fully elucidate trametinib's effectiveness and safety profile in the context of NETs. These studies will help to define the optimal use of trametinib, including the identification of specific NET subtypes most likely to benefit from this therapy, as well as the most effective combination treatment strategies.

Ultimately, the goal of this ongoing research is to establish trametinib's role in the evolving landscape of NET treatment and to improve outcomes for patients affected by this challenging disease(7).

A phase Ib trial (20) assessed the safety and recommended phase II dose of trametinib with everolimus in advanced solid tumors. Sixty-seven patients with advanced solid tumors participated in the open-label, single-arm, dose-escalation study. Common adverse events included mucosal inflammation (40%), stomatitis (25%), fatigue (54%), and diarrhea (42%). Five patients (7%) achieved partial response, and 21 (31%) showed stable disease. The study failed to find a recommended phase II dose with acceptable tolerability and drug exposure. The trial investigated the combination's effect on the RAS/RAF/MEK/ERK and PI3K/mTOR pathways.Trametinib is an oral MEK inhibitor, and everolimus inhibits mTOR. Preclinical data suggested synergistic effects from combining MAPK and PI3K pathway inhibitors. Dose and schedule adjustments were made to reduce mucosal inflammation and stomatitis. Further investigation of this combination is not warranted due to tolerability issues.

NTRK FUSION INHIBITORS

Entrectinib stands as a significant advancement in targeted therapy for neuroendocrine tumors (NETs), specifically those characterized by NTRK gene fusions. These NTRK gene fusions arise from chromosomal rearrangements, leading to the creation of chimeric proteins that possess constitutively active kinase activity. This uncontrolled kinase activity fuels uncontrolled cell growth and proliferation, contributing significantly to the development and progression of NETs. Entrectinib acts as a potent inhibitor of these TRK fusion proteins, effectively blocking the aberrant signaling pathways responsible for tumor growth (8).

By targeting these specific genetic abnormalities, entrectinib offers a more precise and potentially less toxic treatment approach compared to traditional chemotherapy regimens. This targeted approach is

particularly relevant for patients whose NETs harbor these specific NTRK fusions, providing a potential avenue for improved outcomes. The identification of NTRK fusions through comprehensive genomic profiling is crucial for selecting appropriate candidates for entrectinib therapy.

Sigal et al.(21) reported a patient with metastatic neuroendocrine tumor (NET) which showed ETV6:NTRK3 fusion. The patient participated in the STARTRK2 trial (NCT02568267). Entrectinib, a TRK inhibitor, was used to treat the patient. The patient experienced rapid clinical improvement with entrectinib. This was the first reported NTRK fusion in NETs. The tumor initially showed pseudoprogression before responding to treatment. Further research is needed to determine the prevalence of NTRK fusions in NETs.

Larotrectinib and entrectinib represent significant advancements in targeted cancer therapy, specifically designed for the treatment of tumors exhibiting NTRK gene fusions. These fusions result in the production of aberrant TRK proteins, which drive the growth and proliferation of cancerous cells. While both larotrectinib and entrectinib target these TRK proteins, effectively inhibiting their activity, key distinctions in their mechanisms of action and clinical profiles warrant careful consideration. This analysis will delve into a comparative overview of these two targeted therapies, highlighting their similarities and differences(9).

Larotrectinib is characterized by its remarkable selectivity for TRK proteins. This focused targeting translates to a high degree of precision in inhibiting the activity of TRK fusion proteins, minimizing off-target effects and potentially reducing the risk of adverse events. This precision makes larotrectinib a potent inhibitor of tumor growth in cancers driven by NTRK fusions, regardless of the tumor's tissue of origin. The drug's highly selective nature contributes to its distinct safety and efficacy profile.

In contrast, entrectinib exhibits a broader spectrum of activity. While it effectively targets TRK proteins, similar to larotrectinib, it also inhibits other tyrosine kinases, including ROS1 and ALK. This broader targeting profile can be advantageous in patients whose tumors harbor multiple oncogenic drivers, potentially offering a more comprehensive therapeutic approach. For instance, patients with tumors exhibiting both NTRK and ROS1 fusions may benefit from the multi-targeted approach of entrectinib. However, this broader activity also contributes to a distinct side effect profile compared to larotrectinib. The inhibition of ROS1 and ALK can lead to specific adverse events that are not typically observed with larotrectinib, requiring careful monitoring and management.

Clinical trials have demonstrated the efficacy of both larotrectinib and entrectinib in patients with NTRK fusion-positive cancers, showcasing their ability to induce significant tumor regression and improve patient outcomes. These trials have enrolled patients with a diverse range of tumor types, highlighting the potential of these targeted therapies across various cancer indications. The responses observed in these trials underscore the importance of identifying NTRK fusions as actionable targets in cancer treatment(10).

A phase II trial (22) investigated larotrectinib in advanced cancers with NTRK fusions or overexpression.Seventeen patients received larotrectinib; one group had NTRK fusions, the other, overexpression. The objective response rate was 6%; an additional 25% showed a time-to-progression ratio ≥1.3. Larotrectinib showed limited efficacy in NTRK-overexpressing tumors, unlike in fusion-positive cancers. One patient with an NTRK fusion achieved a durable response; most with overexpression showed no response. Three patients with squamous cell carcinoma achieved a TTP2/1 ratio ≥1.3, indicating disease stabilization.Molecular eligibility allowed a pan-cancer approach, including rare cancers like desmoplastic small round cell tumors. No new safety concerns emerged; 14

grade 3/4 adverse events occurred in 7 patients, but no serious larotrectinib-related events.Median progression-free survival was 3.5 months, and overall survival was 15.9 months. The study concludes larotrectinib lacks clinical activity in NTRK-overexpressing tumors.

Further research and ongoing clinical experience are essential to fully define the optimal use of each agent. Comparative studies directly evaluating larotrectinib and entrectinib head-to-head are needed to provide a more definitive understanding of their relative efficacy and safety profiles in specific patient populations. Additionally, research exploring potential resistance mechanisms to these targeted therapies and strategies to overcome resistance is crucial for maximizing their long-term clinical benefit. The ongoing accumulation of clinical data will continue to refine our understanding of the optimal application of larotrectinib and entrectinib in the evolving landscape of precision oncology.

Repotrectinib, an investigational tyrosine kinase inhibitor (TKI), is under investigation for the treatment of cancers driven by ROS1 and NTRK gene alterations. These alterations can result in uncontrolled cellular proliferation and tumor development. Repotrectinib is designed to inhibit the activity of these altered proteins, potentially mitigating or halting cancer progression. Ongoing clinical trials are evaluating repotrectinib's safety and efficacy in patients with ROS1-positive and NTRK-positive cancers, including non-small cell lung cancer (NSCLC)(11).

A case reported by Chen et al.(23) highlighted the potential of sequential TRK inhibitor therapy and the need for next-generation inhibitors.NTRK gene rearrangements drive oncogenesis in solid malignancies. First-generation TRK inhibitors (larotrectinib, entrectinib) are approved for NTRK fusion-positive tumors. Resistance to first-generation TRK inhibitors arises from on-target and off-target mechanisms. Second-generation TRK inhibitors (repotrectinib, selitrectinib) overcome on-target resistance. A case study details a patient with ETV6-NTRK3 fusion-positive cancer. The patient responded to repotrectinib after failing larotrectinib and selitrectinib. Repotrectinib showed efficacy despite prior chemotherapy and immunotherapy. Repotrectinib's compact structure and binding mechanism explain its effectiveness. Rechallenge with a second-generation TKI after a drug-free period may lead to resensitization.

TARGETTED THERAPY AGAINST RET GENE FUSION

Selpercatinib has shown significant promise in the treatment of RET-fusion-positive neuroendocrine tumors, demonstrating clinically meaningful and durable responses in patients with this specific genetic alteration. These tumors, originating from neuroendocrine cells, are characterized by the presence of RET gene fusions, which drive their uncontrolled growth. Selpercatinib, a highly selective RET inhibitor, targets these fusions, effectively blocking the signaling pathways responsible for tumor proliferation and survival. Clinical trials have demonstrated high response rates and prolonged progression-free survival in patients treated with selpercatinib, offering a new targeted therapy option for individuals with RET-fusion-positive neuroendocrine tumors, including those who have progressed on prior therapies. The efficacy and safety profile of selpercatinib establish it as a valuable advancement in the treatment landscape for this challenging cancer type. Further research is ongoing to explore its potential use in combination with other therapies and to further refine patient selection strategies(12).

A phase 3 trial (24) compared selpercatinib to cabozantinib/vandetanib in advanced RET-mutant medullary thyroid cancer.291 patients were randomized; 193 received selpercatinib, 98 received cabozantinib or vandetanib The primary endpoint was progression-free survival (PFS), assessed by blinded independent central review. Selpercatinib showed superior PFS (not reached vs 16.8 months) and treatment failure–free survival. 12-month PFS rates were 86.8% for selpercatinib and 65.7% for the

control group. Overall response rate was 69.4% in the selpercatinib group and 38.8% in the control group. Selpercatinib had a better safety profile; fewer adverse events led to dose reduction or discontinuation. .Median follow-up was 12 months.The study concluded selpercatinib is superior to cabozantinib/vandetanib.

TARGETTING MULTIPLE PATHWAYS

Cabozantinib is a tyrosine kinase inhibitor targeting multiple receptors, including MET, VEGFR2, and RET, implicated in the development and progression of various cancers, including neuroendocrine tumors (NETs). Clinical trials have investigated cabozantinib's efficacy in specific NET subtypes, demonstrating promising results in some cases. For instance, the CELESTIAL trial showed improved progression-free survival in patients with advanced medullary thyroid cancer, a type of NET. Further research is ongoing to fully elucidate cabozantinib's potential and optimal use in managing different NET subtypes(13).

A Phase three Trial (25) investigated cabozantinib's efficacy in treating advanced neuroendocrine tumors.Two patient cohorts participated: extrapancreatic and pancreatic neuroendocrine tumor patients. Patients were randomly assigned cabozantinib (60mg daily) or placebo. Cabozantinib significantly improved progression-free survival in both cohorts compared to placebo. Objective response rates were higher in the cabozantinib group. Grade 3 or higher adverse events were more frequent in the cabozantinib group. Common adverse events included hypertension, fatigue, diarrhea, and thromboembolic events.

Sunitinib malate is a multi-targeted receptor tyrosine kinase inhibitor, meaning it acts by blocking the activity of multiple cellular enzymes known as tyrosine kinases. These enzymes play crucial roles in various cellular processes, including cell growth, differentiation, and survival. In the context of cancer treatment, inhibiting these kinases can disrupt the signaling pathways that drive tumor growth and progression. Sunitinib specifically targets several receptors, including vascular endothelial growth factor receptors (VEGFRs), platelet-derived growth factor receptors (PDGFRs), stem cell factor receptor (c-KIT), and FMS-like tyrosine kinase 3 (FLT3). This multi-targeted approach makes sunitinib effective against a range of tumor types, including certain subtypes of neuroendocrine tumors (NETs). Neuroendocrine tumors are a heterogeneous group of cancers that originate from neuroendocrine cells, which are specialized cells found throughout the body. These tumors can vary significantly in their location, aggressiveness, and response to treatment(14).

Sunitinib's efficacy was evaluated in a phase II study (26) on advanced neuroendocrine tumor patients. Patients received 6-week sunitinib cycles (50mg/day for 4 weeks, then 2 weeks off). Pancreatic neuroendocrine tumor patients showed a 16.7% objective response rate and 68% stable disease. Carcinoid tumor patients had a 2.4% objective response rate and 83% stable disease. Median time to tumor progression was 7.7 months (pancreatic) and 10.2 months (carcinoid). One-year survival rates were 81.1% (pancreatic) and 83.4% (carcinoid). Sunitinib shows antitumor activity in pancreatic neuroendocrine tumors; further research is needed for carcinoid tumors.

Clinical trials have investigated the efficacy of sunitinib in various NET subtypes, with a particular focus on pancreatic neuroendocrine tumors (pNETs). These studies have demonstrated that sunitinib can provide clinical benefit in some patients with advanced pNETs, particularly those with progressive disease. The mechanism of action in pNETs likely involves inhibiting angiogenesis, the formation of new blood vessels that supply the tumor with nutrients and oxygen, thereby slowing tumor growth.

While sunitinib is not considered a first-line therapy for all NETs, it may be considered a valuable treatment option in specific situations. The decision to use sunitinib is typically based on factors such as the specific NET subtype, the stage and grade of the tumor, the patient's overall health, and prior treatments received. For instance, in patients with advanced, well-differentiated pNETs that have progressed despite other therapies, sunitinib can offer a potential avenue for disease control and symptom management. It's important to note that the response to sunitinib can vary among individuals, and treatment decisions should be made in consultation with a healthcare professional experienced in managing NETs. They can assess the individual patient's characteristics and determine the most appropriate treatment strategy(15).

Optimal tyrosine kinase inhibitor (TKI) selection and dosing are crucial for maximizing treatment efficacy while minimizing potential toxicities and adverse events. A carefully chosen TKI, administered at the most appropriate dose, can significantly improve patient outcomes and quality of life. While TKIs are often initially administered at a standard fixed dose, a personalized approach to dose determination is essential for developing an optimal TKI regimen. This personalized approach should consider various patient-specific factors, including age, weight, comorbidities, concomitant medications, and genetic variations that may influence drug metabolism and clearance. Furthermore, the disease itself, its stage, and the presence of specific mutations can also impact the optimal TKI dose(16,17)

The complex interplay of pharmacokinetic (PK) and pharmacodynamic (PD) processes governing TKI activity must be carefully considered when titrating the optimal dosage. Pharmacokinetics, which describes the body's effect on the drug, encompasses absorption, distribution, metabolism, and excretion. Understanding how these processes vary between individuals is crucial for predicting drug levels and potential toxicities. For example, variations in drug metabolism enzymes can lead to significant differences in TKI plasma concentrations, necessitating dose adjustments to achieve therapeutic levels without exceeding the threshold for toxicity. Pharmacodynamics, on the other hand, describes the drug's effect on the body, including its interaction with the target kinase and downstream signaling pathways. The relationship between drug concentration and its effect on the target kinase is essential for determining the optimal therapeutic window.

Therefore, achieving the optimal TKI dosage requires a comprehensive understanding of both PK and PD principles. Therapeutic drug monitoring, which involves measuring drug levels in the blood, can be a valuable tool for guiding dose adjustments, particularly in patients with complex clinical scenarios or those experiencing adverse events(18). By carefully considering these factors and employing a personalized approach to dosing, clinicians can maximize the benefits of TKIs while minimizing the risk of adverse events, ultimately leading to improved patient outcomes in the treatment of various cancers and other diseases. Regular monitoring and open communication between the patient and healthcare provider are also essential for ongoing assessment and optimization of the TKI regimen.

CONCLUSION

Tyrosine kinase inhibitors (TKIs) have shown considerable promise in treating neuroendocrine tumors (NETs), offering a targeted approach to managing this complex disease. TKIs work by blocking specific enzymes, tyrosine kinases, that play a crucial role in the growth and proliferation of tumor cells. In NETs, these kinases can be overactive, driving uncontrolled cell division and tumor development. By inhibiting these enzymes, TKIs can help slow or stop tumor growth, and in some cases, even shrink existing tumors. Several clinical trials have investigated the efficacy of various TKIs in different types

of NETs, demonstrating positive outcomes in terms of progression-free survival and overall survival. Further research is ongoing to refine the use of TKIs in NET treatment, exploring optimal dosing strategies, combination therapies, and identifying specific patient populations who are most likely to benefit from this targeted therapeutic approach. The development of TKIs represents a significant advancement in the management of NETs, offering new hope for patients with this challenging condition.

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