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Lestaurtinib

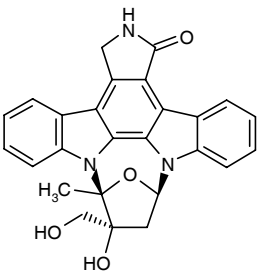
Rec INN; USAN

Multikinase Inhibitor
Oncolytic
Antipsoriatic Agent

CEP-701
KT-5555 (former code name)

9(*S*),12(*R*)-Epoxy-10(*S*)-hydroxy-10-(hydroxymethyl)-9-methyl-2,3,9,10,11,12-hexahydrodiindolo[1,2,3-*fg*:3',2',1'-*kl*]-pyrrolo[3,4-*i*][1,6]benzodiazocin-1-one

InChI=1/C26H21N3O4/c1-25-26(32,12-30)10-18(33-25)28-16-8-4-2-6-13(16)20-21-15(11-27-24(21)31)19-14-7-3-5-9-17(14)29(25)23(19)22(20)28/h2-9,18,30,32H,10-12H2,1H3,(H,27,31)/t18-,25+,26+/m1/s1



$C_{26}H_{21}N_3O_4$
Mol wt: 439.4628

CAS: 111358-88-4

EN: 146816

Abstract

Deregulation of receptor tyrosine kinases is a mechanism for oncogenesis, and the receptors are targets for cancer chemotherapy. Lestaurtinib (CEP-701) is an orally active small-molecule inhibitor of several receptor tyrosine kinases, with specificity for the tropomyosin receptor kinases TrkA, TrkB and TrkC and Fms-like tyrosine kinase 3 (FLT3). Constitutive FLT3-activating mutations are the most frequent genetic event in acute myeloid leukemia (AML), and lestaurtinib inhibits the activity of both mutant and wild-type FLT3. Lestaurtinib is cytotoxic to various human AML cell lines and primary human AML blasts, and prolongs survival in a mouse model of mutant FLT3-dependent leukemia. As monotherapy, lestaurtinib promotes transient hematological responses in patients with relapsed or refractory AML, and the agent is in phase II/III trials in combination with chemotherapeutic agents for the treatment of patients with AML. Lestaurtinib is also being evaluated for the treatment of various other cancers, including neuroblastoma and multiple myeloma, as well as psoriasis.

Synthesis

Lestaurtinib is prepared by selective reduction of the naturally occurring ester analogue K-252a (I) utilizing either $LiAlH_4$ (1, 2) or $LiBH_4$ (3, 4) as the reducing agent. Scheme 1.

Background

Growth factors stimulate the proliferation, migration, differentiation and survival of cells through interactions with specific receptors, and deregulation of growth factor receptor activity is known to be involved in the development of cancer. The receptor tyrosine kinases are a subclass of growth factor receptors that have been successfully targeted for anticancer therapy. For example, trastuzumab (Herceptin®), an inhibitor of the tyrosine kinase HER-2, was approved in 1998 in the U.S. for the treatment of HER-2-overexpressing breast cancer, and imatinib mesilate (Gleevec®, Glivec®), an inhibitor of the tyrosine kinase BCR-ABL, was approved in the U.S. in 2001 for the treatment of Philadelphia chromosome-positive (Ph+) chronic myeloid leukemia (CML). Other receptor tyrosine kinases that have been targeted or are being explored as potential targets include platelet-derived growth factor receptor β (PDGFRβ), Fms-like tyrosine kinase 3 (FLT3), the tropomyosin receptor kinases TrkA, TrkB and TrkC, vascular endothelial growth factor receptor (VEGFR), fibroblast growth factor receptor (FGFR), the stem cell factor receptor Kit, and others (5, 6).

The receptor tyrosine kinases are transmembrane proteins with an extracellular ligand-binding domain and an intracellular catalytic domain with tyrosine kinase activity. In nonproliferating cells, the receptors are maintained in an inactive, nonphosphorylated monomeric form. In some cases, such as FLT3, a juxtamembrane domain also con-

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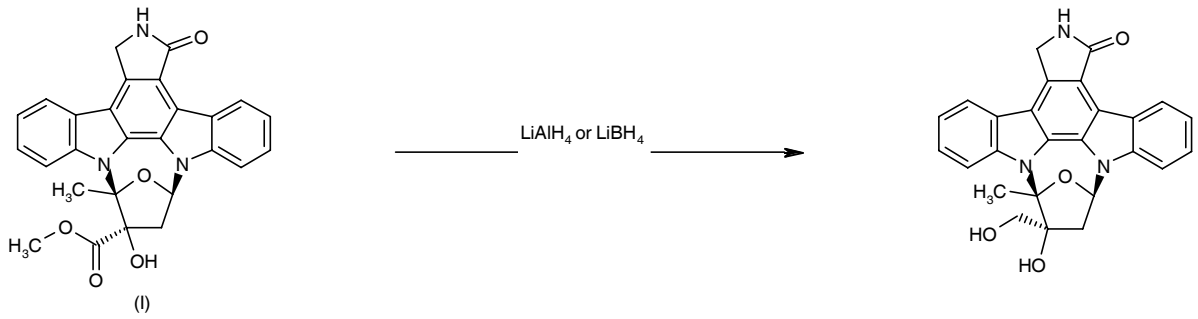
Scheme 1: Synthesis of Lestaurtinib



(I)

tributes to maintaining the enzyme in the inactive form. Upon ligand binding, the receptor oligomerizes and autophosphorylates a key tyrosine residue in the catalytic domain. This allows conformational changes and binding sites are created for target proteins, triggering the activation of signaling pathways. In cancer, receptor tyrosine kinase deregulation can occur through aberrant expression of the receptor or its ligand, and through mutations that cause loss of the tight regulatory mechanisms of the receptor. Either of these mechanisms results in increased receptor signaling and tumorigenesis. An example is FLT3-dependent acute myeloid leukemia (AML). FLT3 is expressed in hematopoietic stem cells, and under normal circumstances, its ligand, produced by bone marrow stroma cells, stimulates myeloblast cells to differentiate and form white blood cells. In AML, differentiation of the myeloblasts is blocked and the cells proliferate in an uncontrolled fashion. FLT3 is aberrantly expressed in 90% of AML cases, and nearly all AML samples also produce FLT3 ligand. This leads to constitutive FLT3 activation by autocrine mechanisms, and the activation of downstream signaling pathways, such as the JAK (Janus kinase)/STAT (signal transducer and activator of transcription) pathway, MAP (mitogen-activated protein)/ERK (extracellular signal-regulated kinase) kinases and the phosphatidylinositol 3-kinase (PI3K)/Akt pathway, regulating cell proliferation, differentiation and apoptosis. In addition to constitutive ligand stimulation, activating mutations of FLT3 occur in about 30% of AML cases and are the most frequent type of genetic alteration found in AML. There are two types of activating mutation: internal tandem duplications in the juxtamembrane regulatory region of the *FLT3* gene (FLT3-ITD), found in 23% of AML cases, and point mutations in the tyrosine kinase domain (most notably in codons 835 and 836) found in 7% of AML cases. These mutations disrupt the tight regulatory mechanisms that normally prevent autophosphorylation, and the receptor becomes active in the absence of ligand binding. In AML, FLT3 activation is associated with enhanced proliferation of immature white blood cells and reduced apoptosis. AML patients with *FLT3* mutations have a particularly poor prognosis for relapse and survival (6-8).

Lestaurtinib (CEP-701) is an orally available, small-molecule tyrosine kinase inhibitor with selectivity for FLT3 and TrkA, TrkB and TrkC over other receptor tyrosine kinases such as VEGFR2/KDR, Kit and PDGFR (4). The agent is in phase II/III trials in patients with relapsed and refractory AML and phase I trials for neuroblastoma. It is also reportedly being evaluated in multiple myeloma. Aberrant T-cell activation in certain autoimmune disorders also appears to depend on receptor tyrosine kinase activity, and lestaurtinib is being evaluated in phase II studies for the treatment of patients with severe psoriasis.

Preclinical Pharmacology

Lestaurtinib potently and selectively inhibited wild-type FLT3 and TrkA kinases in *in vitro* enzyme assays (IC_{50} = 3 and 4 nM, respectively), while showing much less activity against other kinases (IC_{50} = 65, > 500 and 770 nM, respectively, against VEGFR2/KDR, Kit and PDGFR) (8). It also potently inhibited the autophosphorylation of FLT3 in cell-based assays (IC_{50} = 1-2 nM), while exhibiting much less activity against the closely related tyrosine kinases PDGFRβ, Fms and Kit (500-1000 nM or greater) (9-11).

Lestaurtinib selectively inhibited the proliferation of Ba/F3 cells expressing mutant FLT3-ITD (IC_{50} = 5 nM; no effect in parental cells at 200 nM) and human AML-derived cell lines expressing wild-type and mutant *FLT3* genes. STAT5 and ERK1/2 (downstream targets of FLT3) were also inhibited. In primary blasts obtained from AML patients, lestaurtinib (50 nM) inhibited FLT3 phosphorylation in 6 of 7 samples analyzed, and was cytotoxic to 4 of 8 samples, including 3 samples with FLT3-ITD mutations. Using a mouse model of FLT3-ITD leukemia, lestaurtinib 10 mg/kg s.c. every 8 h inhibited FLT3 phosphorylation and significantly and dose-dependently prolonged the survival time (9-11).

When tested against a panel of primary blasts from AML patients, lestaurtinib and midostaurin (PKC-412) exhibited concentration-dependent cytotoxicity, although with significant variability (IC_{50} = 0.001-6.5 μM and 0.42-> 10 μM, respectively); no significant differences

were observed in blasts with wild-type and mutant FLT3 (mean IC_{50} = 0.2 and 0.11 μM, respectively, for lestaurtinib and 7.5 and 4.2 μM, respectively, for midostaurin). Both agents inhibited FLT3 phosphorylation (median IC_{50} = 2.9-3.7 and 11.9 nM, respectively, for lestaurtinib against mutant and wild-type FLT3; median IC_{50} = 5.8-7.7 and 59.8 nM, respectively, for midostaurin). When tested in combination with cytarabine, lestaurtinib was additive to synergistic, particularly in cases of mutant FLT3 (12-14).

Lestaurtinib was also tested against pediatric AML blasts, which included samples with wild-type FLT3, FLT3-ITD mutations and FLT3 point mutations. Cytotoxicity was observed in 93% of the FLT3-ITD samples and 27% and 29% of the FLT3 point mutation and wild-type samples, respectively, although, as with the adults, there was considerable heterogeneity in the cytotoxic response. Addition of FLT3 ligand augmented the sensitivity of a subset of the point mutation and wild-type samples already susceptible to lestaurtinib, although the ligand had no effect on those that were already resistant, nor did it affect the FLT3-ITD population. Among the FLT3-ITD samples, susceptibility was greatest in those with a high mutant/wild-type allelic ratio. Apoptosis was confirmed as the predominant mechanism of cytotoxicity. Cytotoxicity was found to be independent of the FLT3 genotype and the level of FLT3 inhibition by lestaurtinib in these samples. Further analysis showed that in the lestaurtinib-resistant samples, prosurvival signaling pathways were active independent of the level of FLT3 activity (15, 16).

Lestaurtinib showed additive cytotoxicity in combination with cytarabine, daunorubicin or etoposide in cell lines and primary AML blasts harboring FLT3 mutations, whereas antagonistic activity was seen in combination with vincristine (17). In further studies, the combination effect was found to be dependent on the sequence of addition of the agents. Using the FLT3-ITD-expressing cell lines MV-4-11 and Ba/F3/ITD, and an FLT3-ITD-expressing primary blast sample from a patient with AML, lestaurtinib proved synergistic when added concomitantly with or immediately following exposure to cytarabine, daunorubicin, mitoxantrone or etoposide. On the other hand, antagonism was observed if lestaurtinib was added prior to the chemotherapeutic agent. Addition of lestaurtinib alone arrested the cells in the G1/S phase, and it was postulated that when lestaurtinib was added first, the G1/S arrest protected the cells against the toxic effect of subsequently added chemotherapeutic agents (18, 19).

An analysis of primary blast samples from 203 patients with PML-RARA-positive acute promyelocytic leukemia (APL), a subtype of AML, showed that 43% had mutations in the *FLT3* gene (32% had ITD and the remainder point mutations). These patients had a higher rate of induction death than those with wild-type FLT3, although the relapse rate and survival were not different. Using primary blasts from 6 APL patients (4 with FLT3-ITD and 2 with wild-type FLT3), lestaurtinib demonstrated a cytotoxic effect on the FLT3-ITD cells, with evidence of apoptosis, but no significant effect on those expressing wild-type FLT3. Combination of lestaurtinib and *all-trans*-retinoic acid added simultaneously was antagonistic with respect to cytotoxicity and differentiation in the FLT3-ITD blasts (20).

FLT3 is almost universally expressed in B-lineage acute lymphoblastic leukemia (ALL). Lestaurtinib was cytotoxic to and induced apoptosis in 5 of 8 childhood ALL cell lines expressing high levels of phosphorylated FLT3, whereas 3 cell lines with low FLT3 expression were resistant. When incubated with primary childhood ALL samples, apoptosis was observed in 74% of samples that had a high level of FLT3 expression and in only 8% of samples with low FLT3 expression. Cases with rearrangements of the *MLL* gene and cases with high hyperdiploidy express the highest levels of FLT3, and sensitivity to lestaurtinib was particularly high in these samples (82% and 100%, respectively). High sensitivity was also seen in samples with FLT3-ITD mutations, but not in those with point mutations or wild-type FLT3. High sensitivity to lestaurtinib also correlated with a high level of expression of constitutively phosphorylated FLT3. To test the *in vivo* efficacy of lestaurtinib against ALL, primary infant *MLL*-rearranged ALL blasts were injected into mice followed by treatment with lestaurtinib or vehicle. At 14 weeks, the mean engraftment in the bone marrow was 45% in the lestaurtinib-treated mice compared to 96% in the vehicle-treated mice. When tested in combination with daunorubicin, etoposide, vincristine, dexamethasone, cytarabine or L-asparaginase, lestaurtinib was synergistic when added after, additive when added with and antagonistic when added prior to the chemotherapeutic agent. This was attributed to the cell cycle-arresting properties of lestaurtinib mediated by the effect on FLT3 signaling, which may reduce the sensitivity to chemotherapeutic agents (21-25).

The FLT3-ITD mutation not only induces proliferative and antiapoptotic pathways, but also blocks the differentiation of myeloid cells in response to granulocyte colony-stimulating factor (G-CSF). Addition of 5 nM lestaurtinib to 32Dcl3 cells (a murine myeloid cell line expressing FLT3-ITD) inhibited the FLT3-ITD kinase activity, downregulated STAT5 and STAT3 protein expression, inhibited STAT5 phosphorylation, and abrogated the block in G-CSF-dependent cell differentiation. Overcoming the block in maturation was coincident with an antiproliferative effect of lestaurtinib and increased apoptosis in these cells. Thus, overcoming the block to maturation may be one of the antileukemic mechanisms of lestaurtinib (26-28).

Recent *in vitro* experiments indicated the potential of lestaurtinib in patients with myeloproliferative disorders. The compound was found to potently inhibit wild-type JAK2 (Janus kinase 2) enzyme activity (IC_{50} = 1 nM), as well as constitutive JAK2/STAT5 signaling (IC_{50} = 10 nM) and growth of human erythroleukemia HEL 92.1.7 cells with the V617F JAK2 mutation (IC_{50} = 30-100 nM), and the growth of erythroleukemia xenografts in nude mice. Using $CD34^+$ peripheral blood cells from patients with myeloproliferative disorders cultured under conditions favoring erythroid proliferation, lestaurtinib at concentra-

tions of 100 nM or less significantly inhibited the growth of cells from 2 of 4 patients with polycythemia vera, 10 of 11 patients with essential thrombocythemia, 2 of 2 patients with agnogenic myeloid metaplasia and a patient with AML; it was also active against samples with the V617F mutation, whereas normal $CD34^+$ bone marrow cells were not affected. Inhibition of JAK2/STAT5 and Akt signaling was seen at these concentrations (29).

Lestaurtinib inhibited brain-derived neurotrophic factor (BDNF)-induced TrkB phosphorylation *in vitro*, with complete inhibition at 100-200 nM. In a nude mouse model of TrkB-dependent neuroblastoma, lestaurtinib 20 mg/kg twice daily slowed tumor growth. On day 21, vehicle-treated tumors measured 4.3 cm^3 and lestaurtinib-treated tumors measured 2.1 cm^3; lestaurtinib also significantly prolonged survival. Lestaurtinib enhanced the effects of cyclophosphamide, cyclophosphamide + topotecan and 13-*cis*-retinoic acid in this model (30, 31).

Lestaurtinib inhibited the invasiveness of melanoma cell lines stimulated by nerve growth factor (NGF), the neurotrophin ligand of TrkA. In two mouse models of TrkA-expressing human melanoma xenografts, lestaurtinib prolonged the noninvasive stage of the tumor. In an *in vitro* skin model of TrkA-dependent metastatic melanoma, lestaurtinib inhibited the penetration of melanoma cells into the reconstructed dermis. These findings suggest the possibility of combining the anti-invasive properties of lestaurtinib with antiproliferative therapeutic agents to treat metastatic melanoma (32).

Trk receptors have also been implicated in the invasive phenotype of human pancreatic ductal adenocarcinoma (hPDAC). Lestaurtinib (10 mg/kg s.c. twice daily 5 days a week for 21-28 days) inhibited tumor growth in subcutaneous murine xenograft models (AsPC-1, COLO 357, BxPC-3 and MIA PaCa2) of hPDAC by 50-70% compared to vehicle, without toxicity. Similar results were observed with gemcitabine (2.5 mg/kg i.p. once daily 5 days a week), and the two agents in combination resulted in slightly greater antitumor efficacy than either agent alone. In murine s.c. PANC-1 hPDAC xenografts, lestaurtinib (10 mg/kg s.c. twice daily 5 days a week for 21 days) reduced tumor volume, with a T/C value of 25%. Lestaurtinib also inhibited cell invasion through the tracheal wall in the BxPC-3, AsPC-1 and PANC-1 murine tracheal xenograft models of invasive hPADC. Moderate inhibition of invasiveness was seen with the MIA PaCa2 xenografts, while there was no reduction in invasiveness with CFPAC xenografts (33-36). The efficacy of lestaurtinib (10 mg/kg s.c. once daily) and gemcitabine (100 mg/kg i.p. 3 times a week) alone or in combination was assessed in a nude mouse model of metastatic hPDAC. The median survival on gemcitabine alone was 83 days compared to 129 days in combination with lestaurtinib (37).

Lestaurtinib demonstrated *in vitro* and *in vivo* antitumor activity in a series of prostate cancer models. The neurotrophins and their receptors trkA, trkB, trkC and p75 play an important role in mediating prostate cancer progression, and TrkA and TrkB signaling was shown to be increased in a panel of prostate cancer cell lines and derivatives with varying degrees of proliferation/invasiveness. Lestaurtinib inhibited the neurotrophin-mediated phosphorylation of TrkA, TrkB and TrkC in these cells, and inhibited the NGF (TrkA)- and BDNF (TrkB)-mediated migration and invasiveness of these cells (38).

Preliminary experiments demonstrated that lestaurtinib (10 mg/kg s.c. once or twice daily for 21 days) inhibited tumor growth by over 50% in rats with prostate carcinoma AT-2 and nude mice bearing human prostate carcinoma LNCaP tumor xenografts, which was not due to an antiproliferative effect, but rather to induction of apoptosis. The fast-growing Dunning R-3327 AT6.3 rat prostate cancer model is androgen-independent and associated with a high rate of lung metastasis. Lestaurtinib (10 mg/kg s.c. once daily for 16 days) inhibited primary tumor growth by 70% in this model. Histological analysis showed that there was no difference in the proliferation of tumor cells compared to vehicle-treated animals, but the rate of apoptosis was increased. In other experiments, lestaurtinib decreased the number of lung metastases, which was also due to increased apoptosis rather than inhibition of cell proliferation. Long-term survival was examined in the Dunning R-3327 H model of prostate cancer. Using rats with established cancers, lestaurtinib (10 mg/kg twice a day by oral gavage for 5 days a week) significantly extended median survival. Furthermore, in two mouse models of human androgen-independent prostate cancer (TSU-pr1 and CWR-22Rv1), lestaurtinib (10 mg/kg s.c. twice daily for 5 days a week for 3 weeks) completely prevented tumor growth (39). Further assessment indicated that lestaurtinib induced prostate cancer cell apoptosis via inactivation of survival signaling and delayed elevation in intracellular Ca^{2+} (40, 41).

In the Dunning R-3327 H rat model of prostate cancer, androgen ablation alone using 5.2 mg/kg leuprolide every 3 weeks for 63 days lead to a one-third decrease in the total number of prostate cancer cells relative to day 0. In the same model, lestaurtinib 10 mg/kg by oral gavage twice a day for 5 days a week for 2 cycles of 3 weeks on days 0-20 and 32-53 blocked any significant increase in total tumor cells over the 63-day period. The combination of androgen ablation and lestaurtinib led to a > 80% regression in the total tumor cell number relative to day 0. In a rat model of leuprolide-induced androgen-independent prostate cancer, 15 days of lestaurtinib treatment in addition to leuprolide therapy again caused an 80% decrease in the total tumor cell number relative to day 0 (42).

The antitumor efficacy of lestaurtinib was also examined in a model of human ovarian cancer in SCID mice using the cell line A2780-SEAP13, which secretes alkaline phosphatase into the serum as a marker of tumor burden. Administration of lestaurtinib (10 mg/kg s.c. twice daily for 30 days) reduced tumor volume and serum alkaline phosphatase levels in comparison to vehicle-treated controls. No toxicity was observed in the study (43).

In two human medullary thyroid carcinoma cell lines expressing constitutively activated RET receptor tyrosine kinase, lestaurtinib caused cell cycle arrest and induced

apoptosis. Cytotoxicity correlated with inhibition of RET autophosphorylation, which was concentration-dependent and occurred at concentrations below 100 nM in 0.5% serum (and somewhat higher concentrations in 16% serum). However, lestaurtinib was ineffective when tested in a nude mouse model of medullary thyroid carcinoma xenografts (44).

Aside from its anticancer potential, lestaurtinib is being investigated as an immunomodulatory agent for the treatment of autoimmune disorders, as mature dendritic cells have been shown to express high levels of FLT3, which was inhibited by lestaurtinib. Treatment of both murine and human dendritic cells with lestaurtinib induced apoptosis in a concentration-dependent manner. In a coupled dendritic cell/T-cell proliferation assay, addition of lestaurtinib caused apoptosis of dendritic cells, which in turn prevented T-cell proliferation. *In vivo*, lestaurtinib specifically decreased dendritic cell populations and natural killer (NK) cells in the spleen and lymph nodes of mice, but did not affect the population of B- or T-cells. In a model of autoimmune response, pretreatment of HA137 mice with lestaurtinib protected against the activation of injected 6.5 $CD4^+$ T-cells, whereas vehicle alone was unable to prevent expansion of this T-cell population. Myelin oligodendrocyte glycoprotein (MOG) vaccination was used to establish experimental autoimmune encephalitis (EAE) in mice (a model for multiple sclerosis), and once established, the mice were randomized to receive lestaurtinib or vehicle treatment. Lestaurtinib-treated mice showed significantly improved disease progression *versus* vehicle-treated animals, as well as greater preservation of myelin in tissue removed from the spinal cord, cerebellum and brain. To test the effect of lestaurtinib on the general immune system, mice were pretreated with lestaurtinib or vehicle and then challenged with *Listeria monocytogenes* at LD_{20}. There was no difference between the groups in terms of disease severity or survival, indicating that immune suppression did not inhibit the response to an infectious challenge (45).

Pharmacokinetics and Metabolism

In a phase I dose-escalating study, 30 patients with advanced incurable malignancies received oral lestaurtinib at doses of 5-160 mg twice daily with a 7-day rest period after the first 28 days. Peak plasma concentrations were reached at 1-3 h and there was a greater than dose-proportional increase in serum lestaurtinib levels by day 28 compared to day 1. At day 28, the C_{max} and $AUC_{0\text{-}12h}$ were 4 μg/ml and 26 μg.h/ml, respectively, in the 40-mg cohort, and oral clearance was 3 l/h. There was pronounced interpatient variability in exposure by day 28, with a 60% coefficient of variation for AUC in the 40-mg cohort. No objective tumor responses were seen in any patient (46, 47).

Safety

In the above study, the agent was poorly tolerated above 40 mg twice daily, the most frequent adverse events being nausea (63%), diarrhea (47%), anorexia (37%), asthenia (30%), constipation (27%) and vomiting (27%). Grade 3 nausea was observed in 1 patient at the 80-mg dose, and grade 3 anemia in another patient at the 120-mg dose, and grade 3 events were observed in 2 of 12 patients given 40 mg twice daily, marking this as the maximum tolerated dose (MTD) in this population (46, 47).

Clinical Studies

The hematological effects of lestaurtinib were assessed in an open-label phase I/II trial in patients with refractory, relapsed or poor-risk AML expressing FLT3-activating mutations. Fourteen patients received oral lestaurtinib 60 mg twice daily. Five patients had a measurable clinical response, including reductions in bone marrow and peripheral blood blasts, although the responses were of short duration, lasting from 2 weeks to 3 months. Hematological responses correlated with the extent of FLT3 phosphorylation in samples taken from the patients. The mean trough plasma level of lestaurtinib on day 28 was 1.9 μg/ml (range: 0.5-5.8 μg/ml). Lestaurtinib was well tolerated; the most common adverse events were mild nausea, emesis and generalized weakness and fatigue (48-50).

In an open-label phase II trial of lestaurtinib in 29 older patients (> 60 years) with previously untreated AML and not considered fit for intensive chemotherapy, patients received oral lestaurtinib (60 mg twice daily, escalating to 80 mg twice daily) for 8 weeks. Lestaurtinib was generally well tolerated, and the most common toxicities included mild nausea, emesis, constipation, diarrhea and elevated alkaline phosphatase. Two patients were withdrawn from treatment following dose-limiting toxicities (DLTs) at 60 mg twice daily. Doses were increased to 80 mg twice daily in 19 patients. Grade 3-4 nausea was seen in 2 patients, grade 3-4 diarrhea in 2 patients, and 1 patient died from intracerebral hemorrhage. Of 5 patients with a mutated *FLT3* gene, 3 showed a hematological response, and of 22 with a wild-type *FLT3* gene, 5 showed a response. Clinical responses were seen in patients with both pretreatment blast susceptibility to lestaurtinib and post-treatment sustained FLT3 inhibition. To identify potential biomarkers for the AML patients most likely to respond to lestaurtinib, gene expression profiling experiments are under way (51-53).

A randomized, open-label phase II study assessed lestaurtinib in combination with chemotherapy in patients with relapsed AML and harboring FLT3-activating mutations. Patients were randomized 1:1 to receive chemotherapy alone (mitoxantrone, etoposide and cytarabine in those who had an initial remission duration of < 6 months, and high-dose cytarabine in those with an initial remission of 6-24 months) or chemotherapy with lestaurtinib 80 mg twice daily starting 2 days after the initial chemotherapy dose. Ten of 17 patients randomized to lestaurtinib achieved complete remission or partial response within 42 days of study entry, compared to 4 of 17 on chemotherapy alone. Adverse events included mild

to moderate gastrointestinal symptoms and fatigue. Clinical response correlated with pretreatment leukemia cell susceptibility to lestaurtinib and post-treatment plasma FLT3-inhibitory activity of > 85% (54).

Three clinical trials of lestaurtinib are currently recruiting patients. An ongoing randomized, open-label phase II study of oral lestaurtinib given in sequence with induction chemotherapy aims to determine the proportion of patients with relapsed AML who achieve a second complete remission (55). An open-label phase I dose-finding study at the National Cancer Institute (NCI) is exploring the safety, pharmacokinetics and pharmacodynamics of lestaurtinib in pediatric patients with recurrent or refractory high-risk neuroblastoma (56). A 12-week, open-label, nonrandomized phase II dose-escalation study is exploring the efficacy, safety and tolerability of oral lestaurtinib in patients with severe recalcitrant plaque-type psoriasis (57). The FDA granted orphan drug designation for its use in the treatment of AML in April 2006 (58).

Sources

Cephalon, Inc. (US); originally developed by and licensed from Kyowa Hakko Kogyo Co., Ltd. (JP).

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