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Nelarabine

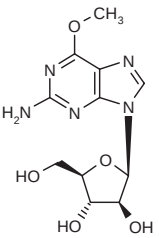
Prop INN; USAN

Lymphoma Therapy
Lymphocytic Leukemia Therapy
Purine Biosynthesis Inhibitor

Nelzarabine (former INN; USAN)
GW-506U
GW-506U78
NSC-686673
Arranon®

9-(β-D-Arabinofuranosyl)-6-methoxy-9*H*-purin-2-amine

9-β-D-Arabinofuranosyl-6-*O*-methylguanine



$C_{11}H_{15}N_5O_5$
Mol wt: 297.2675

CAS: 121032-29-9

EN: 229059

Abstract

Nelarabine (Arranon®) is a water-soluble prodrug of the cytotoxic deoxyguanosine analogue 9-β-D-arabinofuranosylguanine (ara-G). Although not active itself, nelarabine can be demethoxylated by adenosine deaminase to ara-G and subsequently converted to its active 5'-triphosphate (ara-GTP) form. Preclinical studies have shown that accumulation of ara-GTP in leukemic blasts allows for incorporation of ara-GTP into DNA, leading to inhibition of DNA synthesis and cell death. Preclinical and phase I clinical studies demonstrated that nelarabine is toxic to T-cells with much greater potency and specificity compared to other types of leukemic cells. Phase II trials conducted in pediatric and adult patients with acute T-cell lymphoblastic lymphoma (T-LBL) or T-cell acute lymphoblastic leukemia (T-ALL) demonstrated complete response rates of about 20% and a median overall survival of 21 weeks for adults and 13 weeks for children. The most common adverse event related to nelarabine is neurological toxicity. GlaxoSmithKline introduced nelarabine earlier this year following accelerated approval by the FDA in November 2005 for the above indications.

Synthesis

Reaction of uridine (I) with diethyl carbonate and $NaHCO_3$ gives the cyclic ether (II), which is hydrolyzed by means of aqueous NaOH to yield the arabinosyl uracil (III) (1). Reaction of 2-amino-6-chloropurine (IV) with either NaOMe or NaH in MeOH gives 2-amino-6-methoxypurine (V), which is finally submitted to a *trans*-glycosidation process with arabinosyl uracil (III) by means of purine nucleoside phosphorylase and uridine phosphorylase in a potassium phosphate solution at 37 °C (2). Scheme 1.

Background

Leukemia and lymphoma are serious malignancies in children and adults. Lymphoid malignancies involving T-cells, such as T-cell acute lymphoblastic leukemia (T-ALL) and T-cell lymphoblastic lymphoma (T-LBL), are relatively rare but generally aggressive. Early studies showed that T-cell malignancies are not as responsive to chemotherapy as B-cell or other malignancies. Although the treatment of these cancers has improved considerably in recent years, patients who do not respond to standard treatments or who have relapsed have a very poor prognosis. Drugs with better selectivity and greater activity against T-cell lymphoid malignancies are therefore needed (3-5).

It has been observed that purine nucleoside phosphorylase (PNP) deficiency is associated with T-cell lymphopenia, which served as a rationale for the development of nucleoside analogues to treat lymphoid malignancies (3, 6-8). Discovered in the 1970s, the deoxyguanosine analogue 9-β-D-arabinofuranosylguanine (ara-G) exhibited toxicity to T-cells, with accumulation of its active triphosphate form (ara-GTP) in T-cells,

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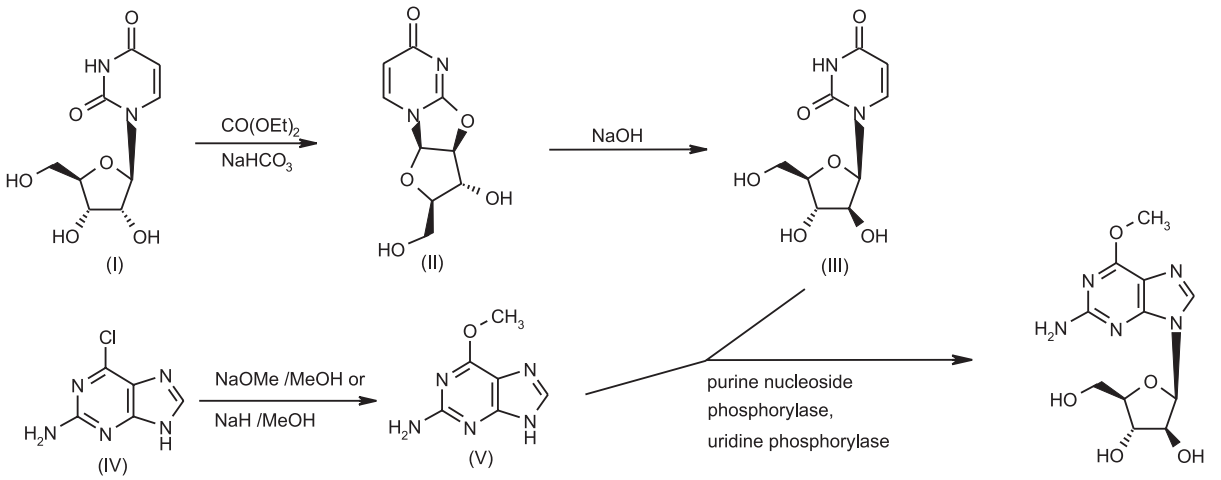
Scheme 1: Synthesis of Nelarabine



resulting in inhibition of DNA synthesis. However, it has not been used in clinical studies due to its poor water solubility and difficult synthesis. With almost 10 times greater solubility than ara-G, its prodrug nelarabine (GW-506U78, 506U78, NSC-686673, Arranon®) was synthesized to address this problem (3, 9, 10).

Preclinical Pharmacology

In vitro studies demonstrated that nelarabine is converted to ara-G by adenosine deaminase. Although no phosphorylation by deoxycytidine kinase could be detected, it was phosphorylated to some extent by adenosine kinase. Nelarabine displayed similar growth-inhibitory activity to ara-G in human T-cell leukemia cell lines and monocytic cell lines, with IC_{50} values of 0.3-0.4, 1.0-1.5 and 0.8 μM, respectively, against CEM, U-937 and Monomac-6 cells, while it was ineffective against B-cell leukemia IM-9 cells (IC_{50} > 100 μM). Further studies indicated that cytotoxicity in human acute leukemia cell lines is directly related to cellular ara-GTP accumulation, and high accumulation of ara-GTP in T-cells leads to apoptosis (11, 12).

L-Asparaginase is known to antagonize the cytotoxic effects of antimetabolites and therefore the effect of asparagine depletion on the cytotoxicity of nelarabine was investigated in human MOLT-4 and CEM T-cell leukemia cell lines. The results demonstrated no effect on the cytotoxicity of nelarabine, with IC_{50} values against MOLT-4 cells of 1.61 and 0.13 μM, respectively, in asparagine-containing and -depleted media, and respective IC_{50} values in CEM cells of 0.87 and < 0.1 μM. Exposure of these cells to both nelarabine and L-asparaginase was associated with complete growth inhibition (13).

In vivo studies in mice showed efficacy against T-cell malignancies and no toxicity (9).

Pharmacokinetics and Metabolism

Studies in cynomolgus monkeys showed that both nelarabine and ara-G were poorly absorbed after oral administration, and the relative bioavailability of ara-G from nelarabine was very low (11%). However, when administered by i.v. infusion, nelarabine was rapidly converted to ara-G, with a t_{max} for ara-G of 30 min and a $t_{1/2}$ of about 2 h. The plasma AUC of ara-G was 9-fold higher than that for nelarabine (9).

Further experiments in cynomolgus monkeys evaluated single and multiple i.v. infusions of nelarabine. In this study, nelarabine was administered as either a single 4-h infusion of 150 mg/kg or as a 1-h infusion of 50 mg/kg/day for 3 consecutive days. The dose-normalized AUC values for nelarabine and ara-G were comparable after single and multiple doses, and the AUC did not change between day 1 and day 3 with repeated administration. The mean plasma concentrations of nelarabine at the end of the infusion were similar with both regimens, whereas the plasma concentrations of ara-G at the end of the infusion following the 4-h infusion were substantially higher than following 1-h infusions. The median plasma half life ($t_{1/2}$) of nelarabine and ara-G was 0.2 and 2 h, respectively. Levels of ara-G in the cerebrospinal fluid (CSF) were 27-47% those in plasma and no accumulation of either compound was detected in CSF or plasma (14).

Clinical pharmacokinetics of nelarabine were evaluated in both pediatric and adult patients with refractory hematological malignancies. Nelarabine at doses ranging from 5 to 75 mg/kg was administered over 1 h. Peak plasma levels of nelarabine were reached at or near the end of the infusion. Both the C_{max} and AUC were proportional to the dose. Children showed higher clearance and steady-state volume of distribution (V_{ss}) of nelarabine compared to adults, whereas values for ara-G were generally similar. The mean $t_{1/2}$ of nelarabine in pediatric and

adult patients was 14.1 and 16.5 min, respectively, and that of ara-G was 2.1 and 3.0 h, respectively. No statistically significant differences in the V_{ss} were observed between children and adult patients. Gender did not affect the pharmacokinetic parameters, and pharmacokinetic parameters for ara-G were similar in patients with different hematological malignancies (15, 16).

The mean C_{max} of the major intracellular metabolite ara-GTP was 23, 42, 85 and 93 μmol/l, respectively, at nelarabine doses of 20, 30, 40 and 60 mg/kg. The concentration of ara-GTP in leukemic cells was higher in patients with T-lymphoblastic disease (median: 140 μmol/l) compared to other diagnoses (median: 50 μmol/l). Also, ara-GTP was generally retained longer in T-leukemic cells than other types of leukemia cells, although in most patients, the $t_{1/2}$ of ara-GTP was > 24 h. Moreover, responders were seen to have higher cellular levels of ara-GTP (median: 157 μmol/l *vs.* 43 μmol/l in nonresponders) (16-18).

Another study examined the pharmacokinetics of nelarabine in 25 patients with indolent leukemia who received nelarabine at doses of 0.8-2.9 g/m^2/day over 1-2 h on different schedules every 21-28 days, together with fludarabine (30 mg/m^2 on days 3 and 5). Pharmacokinetics of nelarabine and ara-G were proportional to dose and similar for all diagnoses. Accumulation of ara-GTP was strongly dependent on diagnosis, however, with especially high cellular levels in B-cell chronic lymphocytic leukemia (B-CLL) and T-cell prolymphocytic leukemia (T-PLL), which appeared to be related to clinical response; elimination of ara-GTP was slow (median $t_{1/2}$ > 24 h) (19).

Safety

In the above-mentioned phase I study in pediatric and adult patients with refractory hematological malignancies, the maximum tolerated dose (MTD) was determined to be 60 and 40 mg/kg/day x 5 days in children and adults, respectively. Dose-limiting neurological toxicity was observed in 72% of the patients, and 50% of the children and 85% of the adults experienced reversible neurotoxicity. Symptoms included somnolence, malaise, fatigue, confusion, gait disorders and hypoesthesia. Nonhematological non-neurologic toxicities were reported in 70% of the patients, the most common being nausea, vomiting, diarrhea, fever and anorexia. Grade 1 and 2 neutropenia and thrombocytopenia were seen in 50% and 76% of pediatric patients and 46% and 42% of adult patients, respectively. No patients with normal marrow function before treatment experienced serious (grade 3 or more) hematological toxicity after the first or subsequent doses of nelarabine. Unlike neurological toxicity, hematological toxicities did not appear to be dose-limiting (20, 21).

In a phase II study of nelarabine, serious neurological toxicity was reported in 18% of the patients (22).

Analysis of data from 39 adult patients with refractory hematological malignancies revealed that the estimated probability of unacceptable neurological toxicity was 0.13, 0.15, 0.20, 0.26, 0.34 and 0.5, respectively, at doses of 5, 10, 20, 30, 40 and 60 mg/kg/day x 5. The MTD was estimated to be 30 mg/kg/day, with a 30% probability of unacceptable neurological toxicity at 35 mg/kg/day (23).

Clinical Studies

The overall response rate in the multicenter phase I study in 93 patients with refractory hematological malignancies was 31%. Major responses were seen in patients with T-cell malignancies, and 54% of patients with T-ALL achieved a complete (23%) or partial response (31%) after 1 or 2 courses of treatment. Responses occurred on all doses. The response rate in patients with B-cell disease was 15% (12 partial responses) but no responses were obtained in patients with nonlymphocytic leukemia (20, 21, 24).

A total of 153 young patients (21 years of age or less) were enrolled in a phase II study to define the response rate of nelarabine in children and young adults with refractory or recurrent T-cell disease. Among the patients, 121 enrolled at the final dose levels. The patients were divided into four groups: 1) at least 25% bone marrow blasts in first relapse; 2) at least 25% bone marrow blasts in second or greater relapse; 3) at least 5% bone marrow blasts and positive CSF; and 4) extramedullary relapse. Nelarabine was administered daily for 5 consecutive days every 3 weeks. The initial dose was 1200 mg/m^2 and the final dose was 650 mg/m^2/day for groups 1 and 2, and 400 mg/m^2/day for groups 3 and 4. In group 1, the total response rate was 55%, including 16 complete responses (CRs) and 2 partial responses (PRs). In group 2, the total response rate was 27%, with 7 CRs and 1 PR. For group 3, the total response rate was 33%, with 5 CRs and 2 PRs. In group 4, 14% of the evaluable patients had a partial response. The results of this study indicate that nelarabine is active as a single agent in the treatment of recurrent T-cell leukemia in children (22, 25). The results from this and several of the following studies are summarized in Table I.

The combination of nelarabine and fludarabine was assessed for efficacy and safety in a pilot trial in 13 patients with hematological malignancies, 9 of whom had indolent leukemias, 2 T-ALL, 1 chronic myelogenous leukemia (CML) and 1 mycosis fungoides. The patients received nelarabine at a dose of 1.2 g/m^2 infused on days 1, 3 and 5 plus fludarabine at a dose of 30 mg/m^2 4 h before nelarabine on days 3 and 5. Partial or complete responses were obtained in 7 patients, 6 of whom had indolent leukemias and 4 of whom had failed prior fludarabine. Responders showed significantly higher median peak intracellular ara-GTP levels than nonresponders. Adverse events included grade 1 and 2 myelosuppression and thrombocytopenia in 9% and 35% of patients, respectively, grade 3 and 4 myelosuppression and thrombocytopenia in 31% and 13%, respectively, as well as 2 cases of grade 3 and 4 muscle weakness and a number of cases of grade 2 neurological toxicity (26, 27).

Table I: Clinical studies of nelarabine (from Prous Science Integrity®).

Indication	Design	Treatments	n	Conclusions	Ref.
Leukemia, acute lymphocytic, Lymphoma, T-cell, Lymphoma, lymphoblastic, Lymphoma, non-Hodgkin's	Open	Nelarabine, 400 mg/m^2 i.v. x 5 d 1x/3 wks Nelarabine, 650 mg/m^2 i.v. x 5 d 1x/3 wks Nelarabine, 900 mg/m^2 i.v. x 5 d 1x/3 wks Nelarabine, 1.2 g/m^2 i.v. x 5 d 1x/3 wks	151	Nelarabine was active in recurrent T-cell malignancies, neurological toxicity being the most significant adverse event	22, 25
Leukemia	Open	Nelarabine, 1.2 g/m^2 i.v. over 1 h on d 1, 3 & 5 → [after 4 h] Fludarabine, 30 mg/m^2 i.v. over 30 min on d 3 & 5 1x/21-28 d	13	The combination of fludarabine and nelarabine demonstrated significant activity and acceptable toxicity in patients with refractory leukemias	26, 27
Leukemia, lymphoblastic, Lymphoma, lymphoblastic	Open	Nelarabine, 1.5 g/m^2 on d 1, 3 & 5	53	Nelarabine was well tolerated and active in heavily pretreated patients with refractory T-lymphoblastic leukemia or T-lymphoblastic lymphoma, with 25 of 53 achieving complete responses	29, 30
Leukemia, lymphoblastic, Lymphoma, lymphoblastic	Open	Nelarabine, 650 mg/m^2 on d 1-5 (n=1) Nelarabine, 1.5 g/m^2 on d 1, 3 & 5 (n=14)	15	Nelarabine was generally well tolerated and associated with a complete response in 9/15 patients with refractory T-lymphoblastic leukemia or lymphoma	31
Lymphoma, B-cell, Lymphoma, T-cell, Lymphoma, non-Hodgkin's	Open	Nelarabine, 1.5 g/m^2 on d 1, 3 & 5 1x/28 d x 6 [max.] cycles	23	Responses were seen in 44% and 33% of patients with T- and B-cell lymphoma, respectively, treated with nelarabine	32-34
Lymphoma, lymphoblastic, Lymphoma, lymphoblastic	Open	Nelarabine, 1.5 g/m^2/d i.v. on d 1, 3 & 5 1x/21 d	40	Nelarabine was well tolerated and showed antitumor activity in patients with acute lymphoblastic leukemia and lymphoma	35
Lymphoma, T-cell	Open	Nelarabine, 1.5 g/m^2/d i.v on d 1, 3 & 5 1x/21 d x cycles 2-8	19	Nelarabine was highly toxic and showed little antitumor activity in patients with untreated cutaneous T-cell lymphoma or refractory or relapsed peripheral T-cell lymphoma	36

The use of nelarabine in patients with mature lymphoid leukemia was examined in another study, both alone and in combination with fludarabine. The overall response rates in patients with T-cell disease (12) and B-cell chronic lymphocytic leukemia (B-CLL) (16) were 25% and 31%, respectively. Toxicity consisted mainly of generally mild somnolence, and some patients developed peripheral neuropathy after multiple courses of treatment (28).

A German study assessed the efficacy of nelarabine as monotherapy (1.5 g/m^2 on days 1, 3 and 5) in 53 heavily pretreated adult patients with relapsed T-ALL and T-LBL. Almost half of the patients (47%; 25 patients) achieved a complete response and partial responses were obtained in 7 (13%). Nineteen of the complete responders were transferred to stem cell transplant within a median of 41 days and 7 maintained a complete response for a median of 13 months. The probability of survival was 16% in all patients, but increased to 27% in patients achieving a complete response. Toxicity was mainly moderate bone marrow suppression and elevated liver enzymes, and neurotoxicity was observed in only 2 patients (29, 30).

A similar study was conducted in 15 heavily pretreated adult patients with relapsed/refractory T-ALL/T-LBL (1.5 g/m^2 on days 1, 3 and 5) and 1 adolescent (650 mg/m^2 on days 1-5). Complete response was achieved by 9 patients (56%), there was 1 unconfirmed complete response and 2 patients achieved a partial response. The most frequent adverse events were bone marrow suppression and increase in liver enzymes, and neurotoxicity was observed in 1 patient. Eight of the complete responders subsequently received an allogeneic stem cell transplant and 7 of these remained in complete response at the time of reporting (31).

Nelarabine was tested in another phase II clinical trial in 23 adults with relapsed or refractory peripheral T-cell lymphoma or indolent B-cell non-Hodgkin's lymphoma (NHL). The drug was administered at a dose of 1.5 g/m^2 i.v. on days 1, 3 and 5 every 28 days for a maximum of 6 cycles. Of the 19 evaluable patients, overall response rates in T-cell NHL and B-cell NHL were 44% and 33%,

respectively, with 2 complete responses in the group with T-cell lymphoma. Median time to progression in responders was 8 months. Two patients experienced moderate to severe neurotoxicity (32-34).

The CALGB Study 19801 enrolled a total of 40 patients, 22 with ALL and 18 with LBL, who received nelarabine 1.5 g/m^2 on days 1, 3 and 5. Thirty-eight patients were evaluable for response, which included 6 complete responses and 2 partial responses in 21 patients with ALL and 4 complete responses in patients with LBL, for an overall response rate of 32%. Neurotoxicity occurred in 2 patients, with resolution in 1 case and no recurrence upon retreatment in the other case. Grade 3 or 4 neutropenia and thrombocytopenia were observed in 43% and 33% of patients, respectively. One-year overall survival was 32% and 1-year disease-free survival 40% (35).

Nelarabine monotherapy was also evaluated in patients with cutaneous T-cell lymphoma (CTCL) or refractory/relapsed peripheral T-cell lymphoma (PTCL) in the CALGB 59901 study. The same dose as above was given every 21 days for a minimum of 2 cycles. Of 19 patients enrolled, there were only 2 partial responses, with an overall response rate of 10.5%. Grade 3 or 4 neurotoxicity occurred in 33% of patients and 2 treatment-related deaths were recorded. The study was closed due to lack of efficacy and toxicity (36).

GlaxoSmithKline launched nelarabine (Arranon® Injection) for the first time in the U.S. on January 24, 2006 for the treatment of patients with T-ALL and T-LBL whose disease has not responded to or has relapsed following treatment with at least two chemotherapy regimens. The product received accelerated approval from the FDA in November 2005 based on complete response rates demonstrated in two phase II trials in patients who had exhausted standard treatment. Nelarabine has orphan drug designation in the U.S. (37, 38).

Source

GlaxoSmithKline plc (GB).

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