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ELACYTARABINE

Rec INN

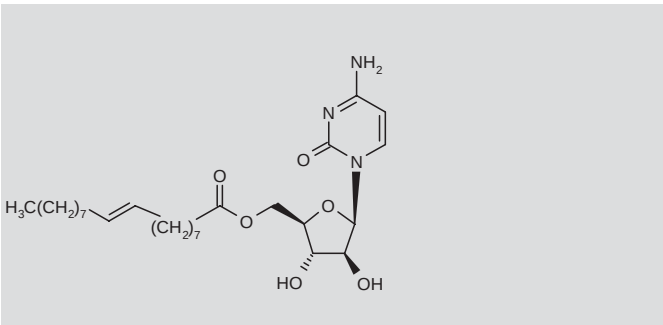
Antimetabolite
Oncolytic

CP-4055
P-4055

4-Amino-1-[5-*O*-[9(*E*)-octadecenoyl]-β-D-arabinofuranosyl]pyrimidin-2(1*H*)-one

5'-*O*-[9(*E*)-Octadecenoyl]-1-β-D-arabinofuranosylcytosine

InChI: 1S/C27H45N3O6/c1-2-3-4-5-6-7-8-9-10-11-12-13-14-15-16-17-23(31)35-20-21-24(32)25(33)26(36-21)30-19-18-22(28)29-27(30)34/h9-10,18-19,21,24-26,32-33H,2-8,11-17,20H2,1H3,(H2,28,29,34)/b10-9+/t21-,24-,25+,26-/m1/s1



$C_{27}H_{45}N_3O_6$
Mol wt: 507.6627
CAS: 188181-42-2
EN: 278822

ABSTRACT

Cytarabine has long been an important component of standard chemotherapy for hematological malignancies. Investigations into the mechanism of resistance to this agent have led to new insights into the metabolism of cytarabine. The human equilibrative nucleoside transporter 1 (hENT1), the principal transmembrane transporter of cytarabine, has been identified as an important mediator of drug resistance. Elacytarabine (CP-4055) is a 5'-elaidic acid ester of cytarabine. A lipophilic derivative, this novel agent enters the cell independent of hENT1 and delivers higher intracellular levels of the active cytarabine metabolite in cells resistant to the parent drug. Preclinical studies of elacytarabine show prolonged intracellular retention and significant cytotoxic activity in cytarabine-resistant models. In clinical studies, elacytarabine has been well tolerated, with early response rates of 15-26.7%. In this review, we present the current status of this new agent and discuss its development from chemical synthesis to clinical studies.

SYNTHESIS**

Elacytarabine is prepared by condensation of cytarabine hydrochloride (I) with elaidoyl chloride (II) in dimethylacetamide (DMA) (1). Scheme 1.

BACKGROUND

Cytarabine (1-β-D-arabinofuranosylcytosine, ara-C, cytosine arabinoside; Fig. 1) has formed the cornerstone of induction therapy for acute myeloid leukemia (AML) for the last three decades (2-4). Hematological malignancies are frequently associated with high cell turnover and are therefore sensitive to the effects of this potent DNA-damaging agent. Its ability to cross the blood brain–barrier has been exploited in the treatment of central nervous system (CNS) lymphomas (5). Response to cytarabine-based induction in AML is dictated by several host factors, such as age, performance status and comorbidity. In addition, the biological features of the disease (the presence of good-, intermediate- and poor-risk karyotypic abnormalities, the expression of multidrug resistance genes and the pres-

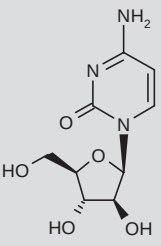


Figure 1. Chemical structure of cytarabine (ara-C).

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**Synthesis prepared by R. Castañer.
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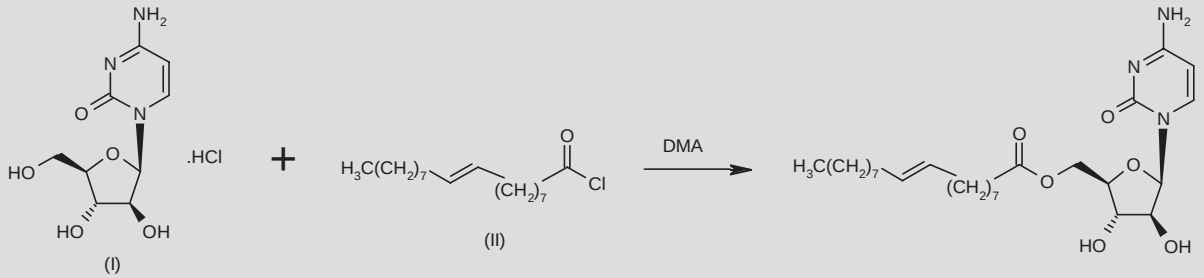
Scheme 1. Synthesis of Elacytarabine



ence or absence of antecedent hematological disorders, among others) account for the significant variation in the long-term survival of patients (6).

First described in 1968 (7), cytarabine is a potent deoxycytidine analogue. The parent compound, deoxycytidine (dCyd), is a nucleoside closely resembling cytidine, but with one less oxygen atom. In its active form, ara-C is a potent but reversible inhibitor of DNA polymerase; however, after longer incubation within the cell, ara-CTP competes with dCyd for incorporation into nucleic acids during replicative and repair DNA synthesis, resulting in irreversible DNA damage and subsequent cell death through apoptosis (8).

Typical for most nucleoside analogues, cytarabine is a hydrophilic compound and relies on active uptake into the cell through specialized nucleoside transporters (human equilibrative nucleoside transporters, hENTs) (9). Four isoforms exist (hENT1-4), and cytarabine is a hENT1 substrate (10-12).

Cytarabine undergoes multiple phosphorylation steps once taken up by the cell. It is converted to a triphosphate pyrimidine nucleoside by the sequential action of three kinases, via deoxycytidine kinase (dCK) to ara-C monophosphate, via deoxycytidylate kinase to ara-C diphosphate and via nucleoside diphosphate kinase to the active metabolite, ara-C triphosphate (ara-CTP) (13, 14). Phosphorylation by dCK is the rate-limiting step in this process (15). The monophosphate intermediate can be dephosphorylated by a cytoplasmic 5′-nucleotidase (5′-NT), known as cN-II, thereby preventing the formation of the active compound (16). The ratio of dCK to 5′-NT in the cell correlates significantly with the production of ara-CTP, and this ratio appears to be more important than the level of either transcript individually (17). Once formed, ara-CTP can be rapidly catabolized by deamination by deoxycytidine deaminase (dCDA) to the nontoxic metabolite 1-β-D-arabinofuranosyluracil (ara-U) (18), which takes place in the blood, liver, kidney and gut (19). The cytotoxicity of cytarabine is predominantly determined by the rate of formation and retention of ara-CTP within the cell (20) (Fig. 2).

The response to ara-C is variable and patients demonstrate both intrinsic and acquired resistance to the drug through several mechanisms: hENT1 deficiency, dCK deficiency, increased 5′-NT expression, dCDA expression and altered DNA polymerase expression being among the most clinically studied (21-27).

Aberrant expression of enzymes involved in the transport/metabolism of ara-C can explain drug resistance to the agent. hENT1 is a member of the equilibrative nucleoside transport family that mediates cellular entry of cytarabine, gemcitabine and fludarabine. In a variety of preclinical models, deficiency in hENT1 confers resistance to these drugs. Several in vitro studies have demonstrated high levels of resistance to ara-C in leukemia cells that are deficient in the hENT1 transport mechanism (28, 29). Early work by Wiley et al. showed that low transport rates correlated with poor clinical responsiveness to ara-C therapy in vivo (30). Hubeek et al. found that in childhood acute myeloid leukemia (AML) hENT1 mRNA expression and ara-C sensitivity were significantly correlated in vivo ($P = 0.001$). AML patients who do not express hENT1 mRNA have a higher risk of early relapse (22). In other experiments, levels of expression of the transporter were lower at first relapse when compared to samples collected at diagnosis (31).

Studies to examine the reasons for a sixfold range in ara-CTP accumulation in AML, acute lymphocytic leukemia (ALL) and T lymphoblastic lymphoma show that activities of cytarabine-metabolizing enzymes are similar among the various leukemia types. However, the number of nucleoside transport sites per cell was significantly different. A significant correlation was observed between the number of transport sites and the accumulation of intracellular ara-CTP (32).

Deoxycytidine kinase is necessary for the phosphorylation of several deoxyribonucleosides and their nucleoside analogues. A deficiency of dCK is associated with resistance to chemotherapeutic agents. Conversely, increased dCK activity is associated with increased activation of these compounds to cytotoxic nucleoside triphosphate derivatives. Several reports (33, 34) implicate dCK activity as a mechanism of resistance to ara-C in preclinical samples; however, the relationship between dCK expression and sensitivity to ara-C has not been clarified in clinical studies. Cell lines resistant to ara-C in vitro have been shown to have decreased or absent levels of dCK activity (33). Transfection of the *DCK* gene into dCK-deficient tumor

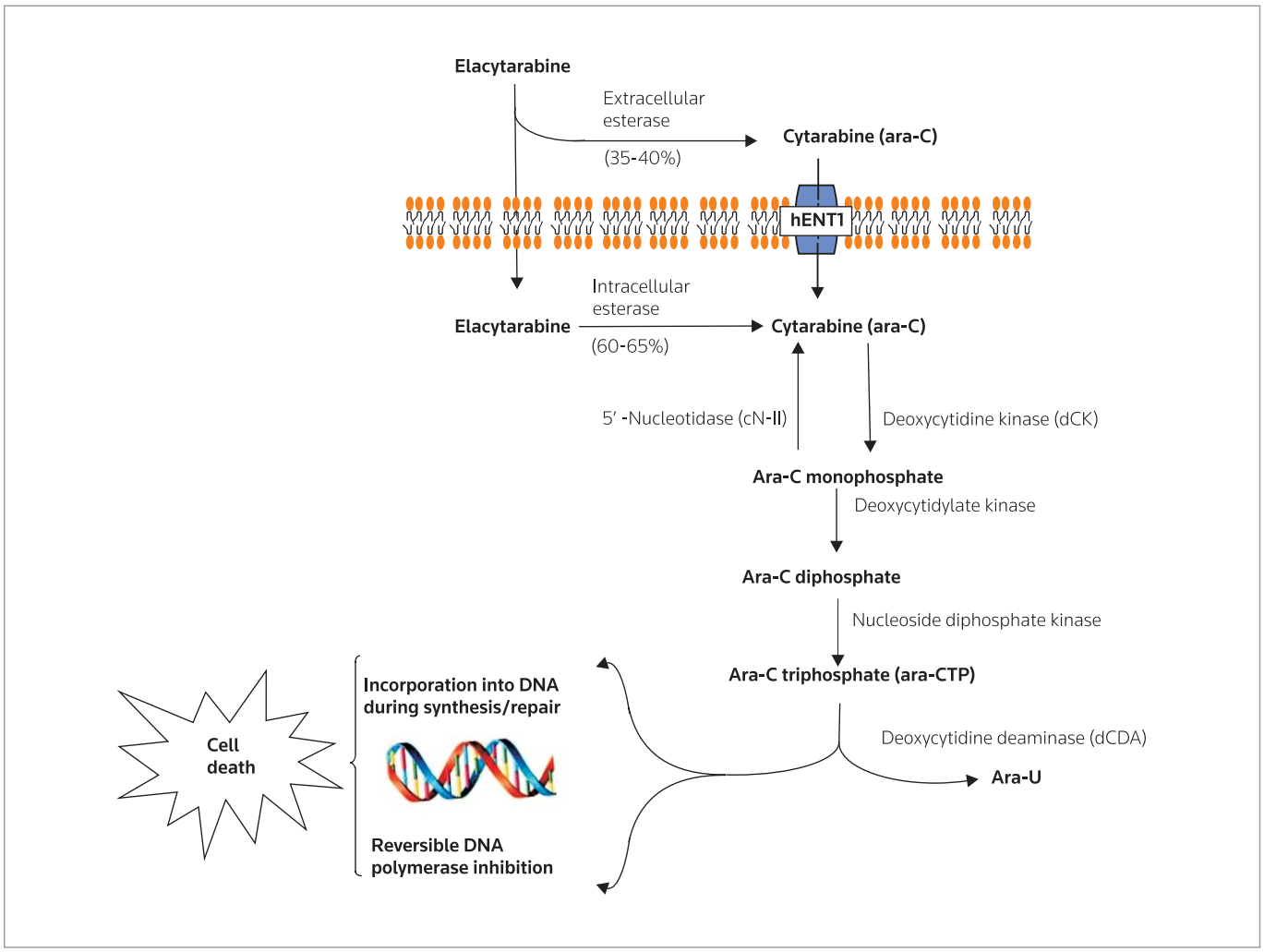


Figure 2. Cellular metabolism of elacytarabine and cytarabine (ara-C). Ara-C is converted to a triphosphate pyrimidine nucleoside by the sequential action of three kinases, deoxycytidine kinase (dCK), deoxycytidylate and nucleoside diphosphate kinase, to the active metabolite ara-C triphosphate (ara-CTP). The monophosphate intermediate can be dephosphorylated by a cytoplasmic 5'-nucleotidase (5'-NT), known as cN-II. Once formed, ara-CTP can be rapidly catabolized by deamination by deoxycytidine deaminase (dCDA) to the nontoxic metabolite 1-β-D-arabinofuranosyluracil (ara-U).

cell lines restored in vitro sensitivity to ara-C (35). DNA sequencing has identified both silent and inactivating mutations of the enzyme in cell lines (36) and in patient samples (24); however, there is controversy in the literature (37). In addition to mutations, alternative dCK mRNA splicing (23) has been proposed as another means of altering enzymatic activity. Despite these in vitro data, large retrospective clinical trial analysis indicates that variation in dCK activity is not predictive of poor outcome with therapy or with adverse prognosis (37).

For cytotoxic activity to occur, ara-C requires activation to its triphosphorylated form, ara-CTP. A 5′-NT dephosphorylates ara-CMP, a key intermediate of this process, preventing accumulation of ara-CTP, which may in turn reduce cellular sensitivity to the effects of ara-C. In vitro, increased activity of 5′-NT is associated with ara-C resistance. 5′-NT activity was significantly increased in the ara-C-resistant human erythroleukemia cell line K-562 compared to sensitive controls. Resistant variants were developed using stepwise increases in the concentration of the nucleoside analogue over a 12-month period (34). In a series of 108 patients with AML, high mRNA levels of the 5′-NT enzyme cN-II in the leukemic blasts at diagnosis were independently correlated with a shorter disease-free survival and with a shorter overall survival in young patients (26). This association needs validation by other groups.

Cytidine deaminase is a pyrimidine salvage pathway enzyme that catalyzes the hydrolytic deamination of cytidine and deoxycytidine to their corresponding uracil nucleosides. Although several studies have been published on the role of increased dCDA activity, its clinical relevance remains controversial. Forced expression of dCDA does confer some resistance in vitro (38), but no convincing evidence suggests this is the case in vivo (21, 39). Once again, the literature appears controversial, with some groups claiming to be able to reverse ara-C resistance through the in vitro administration of

3,4,5,6-tetrahydrouridine, an inhibitor of CDA (40). Others, however, failed when using a similar approach (41).

In a large study in 123 patients, increased levels of DNA polymerase α were found in 39% of patients at diagnosis, which correlated with a shorter disease-free and overall survival (21). In primary patient samples, lower levels of DNA polymerase in AML samples resulted in better cytarabine sensitivity when compared to ALL samples that had much higher levels of this enzyme (42).

In summary, a deficiency of hENT1 is a major determinant of cytarabine resistance. When leukemic blasts were examined at diagnosis for the presence of enzymes involved in ara-C metabolism, 83%, 22%, 7%, 37%, 59%, 37%, 39% and 16% of the patients, respectively, were positive for hENT1, dCK, dCDA, 5′-NT, topoisomerase I, topoisomerase II, DNA polymerase and MDR1 (multidrug-resistant phenotype). This was correlated with response to therapy and the results implicated the expression of hENT1, 5′-NT and DNA polymerase at diagnosis as indicators of related resistance mechanisms to ara-C in AML patients (21).

Given the fact that clinical efficacy of ara-C is wholly dependent on intracellular concentrations of ara-CTP, a strategy to overcome ara-C resistance by developing ara-C analogues that achieved higher and more prolonged intracellular ara-CTP levels was developed. Clavis Pharma generated several ara-C derivatives using their proprietary Lipid Vector Technology (LVT). This technology chemically links specific lipids (lipid vectors) to selected pharmaceutical agents (parent drugs) and the new molecule created is a patentable new chemical entity (NCE). A variety of drug characteristics can be improved by linking lipid moieties to the parent compound (43). Molecules of this sort were tested in four pairs of cell lines that demonstrated resistance to either ara-C or gemcitabine. A clear structure–activity relationship was noted; IC_{50} values increased with chain length and the number of double bonds (44). Eleven derivatives were tested and elacytarabine (CP-4055) was selected as the most active compound and was therefore chosen for further in vivo studies.

PRECLINICAL PHARMACOLOGY

Elacytarabine is the 5′-elaidic acid ester of cytarabine. The added fatty acid has a chain length of 18 carbon atoms and has one double bond at position 9 (C18:1$^{\Delta 9,\ trans}$, unsaturated fatty acid).

The proposed superiority of elacytarabine is based on two pharmacodynamic properties of the drug: its alternative method of cell entry and its retention within the cell. Elacytarabine, unlike ara-C, is not dependent on hENT1 for uptake into the cell (41, 45-47). The addition of the lipid vector, which makes the agent lipophilic, allows it to enter the cell by passive diffusion. When compared to the parent CEM cell line, CEM/araC/8C, a cell line with deficient nucleoside transporters, has been shown to be 56,700-fold more resistant to ara-C but only 75-fold more resistant to elacytarabine. When hENT1-expressing CEM cells were pretreated with nitrobenzylthioinosine (a hENT1 inhibitor), the IC_{50} values increased 720-fold for the ara-C-treated cells and 5.5-fold for elacytarabine-treated cells (47). In other assays, the presence of the transport inhibitors partially reversed the cytostatic activity of cytarabine but not elacytarabine (46).

Elacytarabine is retained longer inside the cell than the parent drug. This was demonstrated when intracellular concentrations of ara-C fell by 40% at 2 h after removal of the drug-containing medium; the intracellular concentration of the derivative, however, had increased 2 h after removal of the drug-containing medium and reached a higher concentration peak (45). Inside the cell, elacytarabine is highly protein-bound, which may be an important factor in its long retention times and more potent DNA-damaging effects compared to cytarabine (41, 45).

The mechanisms for cell death for both cytarabine and its lipid-bound derivative are predictably similar. Both drugs cause S-phase arrest and comparable apoptosis. However, when CEM/araC/8C cells were treated with both drugs, ara-C induced S-phase arrest with little to no apoptosis (5.9% of cells), whereas the derivative mainly induced G_1 arrest and caused apoptosis in a high proportion of the cells (25.8%) (47).

Lipophilic derivatives of ara-C, including elacytarabine, had IC_{50} values equal or slightly higher than ara-C when tested in vitro against a panel of cell lines (41). Activity was also shown in solid tumor xenograft models, where the activity of the novel agent was significantly superior (Fig. 3). Elacytarabine, delivered as daily intrathecal bolus injections and i.p. injections to rodents bearing leukemia xenografts, resulted in statistically significantly longer survival compared with saline control and equimolar cytarabine doses ($P < 0.05$). In other models, partial or complete regression of lung carcinoma and three melanoma xenografts was obtained after treatment with elacytarabine (46).

There are several in vivo reports of synergy between elacytarabine and other anticancer therapies. It has been explored in combination with the monoclonal antibodies (mAbs) bevacizumab, cetuximab and trastuzumab in two human non-small cell lung cancer (NSCLC) xenograft models (EKVX and MAKSAX). Elacytarabine was highly active as monotherapy in MAKSAX, so additive activity with the mAbs could not be distinguished; however, in the EKVX cell line, an additive antitumor effect was seen when it was combined with bevacizumab and trastuzumab, and to a lesser extent with cetuximab (48).

Combinations with docetaxel and oxaliplatin in vitro using the WiDR colon cancer cell line and the A549 non-small cell lung cancer (NSCLC) cell line have been evaluated, as well as in vivo in a Lewis lung metastasis model. Simultaneous exposure in the cytotoxicity assays showed that elacytarabine combined best with oxaliplatin, but it also increased docetaxel-induced cell kill. Simultaneous and sequential dosing was tested and pretreatment with elacytarabine was shown to be preferred (49).

In human leukemia HL-60 cell lines elacytarabine was synergistic when combined with gemcitabine, irinotecan and topotecan, and additive in combination with cloretazine and idarubicin. In U-937 lymphoma cells there was synergy with gemcitabine and an additive effect with other agents. Drug sequence and ratios have also been studied in depth and will provide guidance for further clinical combination studies (50).

PHARMACOKINETICS AND METABOLISM

Elacytarabine is a prodrug; hydrolytic cleavage of the elaidic acid moiety by either an intra- or extracellular esterase generates the

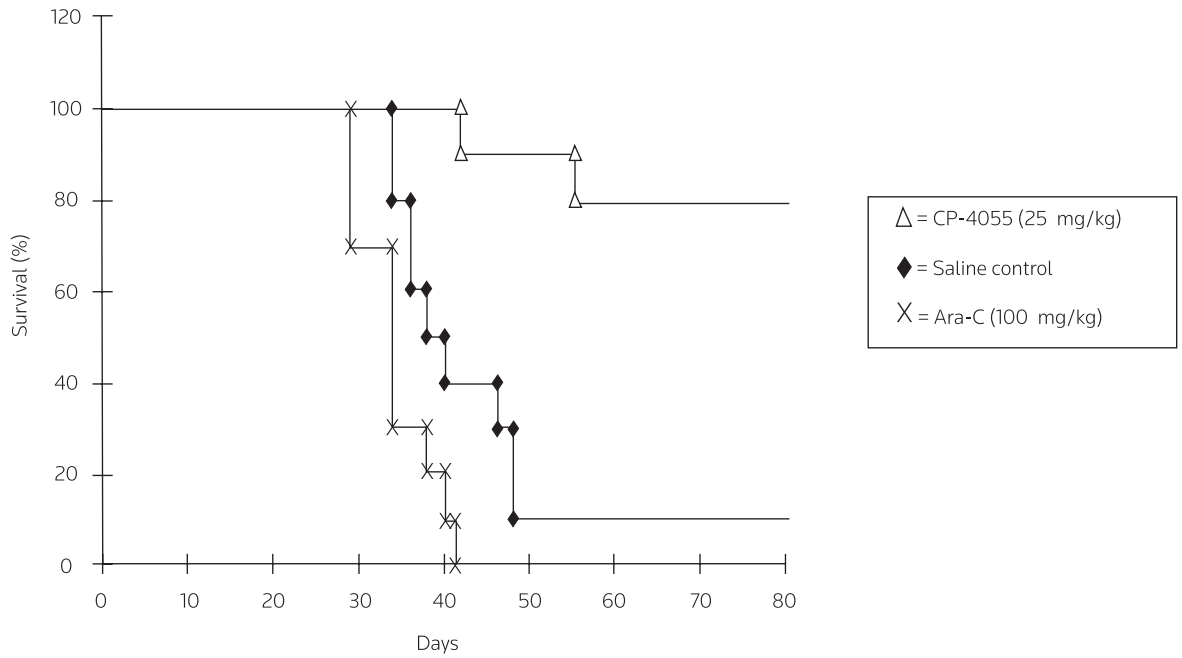


Figure 3. Survival curves constructed from results obtained in experimental metastasis models after injection of 1 x 10^6 Raji lymphoma cells to groups of 10 animals: saline control (◆); 25 mg/kg elacytarabine, days 7-11, 14-18, 21-25 and 28-32 (Δ); and 100 mg/kg cytarabine, days 7-11, 14-18, 21-25 and 28-32 (X). Adapted with permission from: Breistol, K., Balzarini, J., Sandvold, M.L., Myhren, F., Martinsen, M., De Clercq, E., Fodstad, O. *Antitumor activity of P-4955 (elaidic acid-cytarabine) compared to cytarabine in metastatic and s.c. human tumor xenograft models*. Cancer Res 1999, 59(12): 2944-9 (Figure 2).

active drug. Up to 45% of this process occurs extracellularly (45). Raymond et al. combined pharmacokinetic (PK) data from two European phase I trials. Thirty-seven and 21 patients, respectively, were evaluable for day 1 and day 4 PK data collection. The area under the curve (AUC) for elacytarabine increased linearly, as did the maximum plasma concentrations of elacytarabine, ara-C and ara-U, and the data were comparable on days 1 and 4. Interpatient variation was low (mostly < 30%), except for half-lives (> 80%). Plasma elimination was biphasic for doses > 30 mg/m^2 by infusion. Elacytarabine and ara-C were undetectable in most patients at 24 h, while ara-U elimination was slower (51). Although a high percentage of elacytarabine was cleared from the plasma quickly, low concentrations were observed for between 10 and 24 h after infusion in the majority of patients. This was supported by data that showed that elacytarabine was maintained in plasma for up to 5-10 h at dose levels > 150 mg/m^2/day (52). Following dosing with elacytarabine, ara-C levels rapidly increase in the plasma but quickly begin to fall, coincident with a sustained rise in ara-U, and the ara-U/ara-C AUC ratio in these patients exceed by threefold the standard ara-U/ara-C ratio (53).

SAFETY

The maximum tolerated dose (MTD) in mice bearing s.c. melanoma xenografts was 30 mg/m^2/day for 5 days. Continued treatment at this dose for 10 days was toxic (general deconditioning, significant weight loss and one death). A once-daily injection, repeated for 5 days, with a recovery period of 2 days before the next cycle, was found to be optimal, and when administered as such over a 28-day period was generally well tolerated; there was weight loss, indicating that this approached the MTD, but there were no toxic deaths (46). Combination treatment with elacytarabine and mAbs in rodent models was well tolerated, with no increased toxicity in terms of weight loss compared to monotherapy (48).

No significant unexpected adverse events have been reported in humans. In the solid tumor trials, the most common adverse events were fatigue, nausea, vomiting, anorexia, headache, anemia and neutropenia. The latter accounted for the majority of grade III/IV adverse events. One phase I study reported two dose-limiting toxicities (grade III fatigue and grade IV neutropenia) (54). There have been no clear associations between dosing schedule and rate of adverse events.

The hematological malignancy trials have reported nausea and vomiting as the main grade I/II adverse events. The most frequent grade III/IV events were thrombocytopenia, leukopenia, febrile neutropenia, lymphopenia, fatigue and pyrexia. Typhilitis, hand–foot syndrome, tumor lysis syndrome and *Klebsiella* infection were each reported as a related adverse event in the trial combining elacytarabine and idarubicin (55). Typhilitis and hand–foot syndrome were recorded as dose-limiting toxicities. Pyrexia and a rise in hepatic transaminase were reported as serious adverse events in the phase I monotherapy trial and the latter was considered a dose-limiting toxicity (56).

Table I. *Clinical trials of elacytarabine (Source: www.clinicaltrials.gov, meeting abstracts).*

Disease type	Phase	Dose	Comments
Refractory/relapsed hematological malignancies with or without idarubicin	Phase I	200-2500 mg/m^2/day by 2-4-h i.v. or 24-h continuous i.v. infusion on days 1-5 q3w either alone or with idarubicin i.v.	MTD: 2500 mg/m^2/day DLT: hepatic dysfunction
Second salvage acute myeloid leukemia	Phase II	2000 mg/m^2/day by continuous i.v. infusion on days 1-5 q3w	Ongoing
Solid tumors (ovarian cancer, malignant melanoma and advanced non-small cell lung carcinoma)	Phase I	30-240 mg/m^2/day by 30-min or 2-h infusion on days 1-5 q3w or q4w	Neutropenic nadir was 18-26 days, precluding recommendation of 3-weekly schedule
Solid tumors (ovarian cancer, malignant melanoma and advanced non-small cell lung carcinoma)	Phase I	100-480 mg/m^2 by 2-h infusion according to three different schedules: A, days 1 & 8 q3w; B, days 1 & 15 q4w; C: days 1, 8 & 15 q4w	
Second-line therapy in advanced colorectal cancer	Phase II	200 mg/m^2/day by 30-min i.v. infusion on days 1-5 q4w	
Platinum-resistant ovarian cancer	Phase II	Dose not available, i.v. infusion on days 1-5 and days 8-12 q4w	Ongoing
Metastatic malignant melanoma in combination with sorafenib	Phase II	200 mg/m^2/day by 30-min i.v. infusion on days 1-5 q4w	Sorafenib dose 800 mg/day
Previously untreated malignant melanoma	Phase II	200 mg/m^2/day on days 1-5 q4w	

MTD, maximum tolerated dose; DLT, dose-limiting toxicity.

CLINICAL STUDIES

There have been two phase I and four phase II trials in solid tumors (Table I). The first phase I trial was reported this year (52). Thirty-four patients were treated with the drug (19 malignant melanomas, 8 ovarian cancers and 7 NSCLC) with doses ranging from 30 to 240 mg/m^2/day on days 1-5 given either every 3 or 4 weeks as either a 30-min or a 2-h infusion. The MTD was 200 mg/m^2/day for the 3-weekly schedule and 240 mg/m^2/day for the 4-weekly schedule and was independent of infusion duration. The neutropenic nadir was between 18 and 26 days; therefore, the 3-weekly schedule was not evaluated further. The recommended dose to be carried through to phase II testing was 200 mg/m^2/day given on days 1-5 on a 4-weekly schedule. Stable disease (SD) was reported in 9 patients, which lasted between 6 weeks and 13 months. SD was reported in all tumor types, including a patient with stage IV NSCLC treated with 60 mg/m^2/day who had complete resolution of a pleural effusion lasting 13 months. Another objective partial response was reported in a patient with malignant melanoma, with a time to progression of 22 months. One ovarian cancer patient had a reduction in CA125 from 189 to 83, with stable disease for 2.5 months (52, 54, 57).

A second multiple-schedule, dose-escalating phase I trial was conducted with the intention of determining the MTD and optimal schedule for further combination studies. When interval results were reported (53, 58), 45 patients with a variety of tumor types (mainly colorectal, breast and head and neck) had been treated in 4 European centers. There was preliminary evidence of efficacy and the MTD was 440 mg/m^2/week. Of 41 assessable patients, 10 patients had stable disease, lasting longer than 6 months in 4 patients (2 NSCLC, 1 colorectal and 1 kidney).

A phase I study of elacytarabine was carried out to determine the MTD and the preferred infusion time in patients with hematological malignancies. The latest interval report recommends 2000 mg/m^2/day on days 1-5 on a 3-weekly schedule as the monotherapy dose based on data from 77 patients (55). Clinical activity was seen, with manageable nonhematological toxicities. Of 66 evaluable patients, 1 AML patient had a complete response which was maintained after 4 cycles, another AML patient had a partial complete response and 2 partial responses were reported in AML patients at doses of 875-2000 mg/m^2/day for > 2 courses of therapy.

A separate phase I/II study is currently exploring the activity of elacytarabine in combination with idarubicin (fixed dose of 12 mg/m^2/day) for AML patients in first relapse. The MTD of elacytarabine in the combination was 1150 mg/m^2/day (56). Most recent data report manageable toxicity with the combination and recommend dosing at 1000 mg/m^2/day given as a continuous i.v. infusion on days 1-5 every 3 weeks. Among 15 patients, there were 4 responders (overall response rate = 26.7%), 3 complete responses and 1 partial complete response at 1000 mg/m^2/day (59). Phase II studies of the combination are planned.

Phase II trials have been carried out for three indications –malignant melanoma, colorectal cancer and ovarian cancer. Treatment of malignant melanoma has been studied using elacytarabine alone (NCT00232726, CP4055-201) and in combination with sorafenib (NCT00498836, CP4055-203). In the latter trial, elacytarabine was administered on days 1-5 every 4 weeks as a 30-min infusion. The initial starting dose was 150 mg/m^2/day (3 patients) and continued at 200 mg/m^2/day. Preliminary results showed that the combination was well tolerated. The study was completed in October 2008

and full results are awaited. Another study evaluated patients with metastatic colorectal cancer who had failed a first-line chemotherapeutic regimen containing oxaliplatin and 5-fluorouracil (5-FU), with or without bevacizumab or other investigational medicinal products (NCT00498407, CP4055-202). They received elacytarabine alone at 200 mg/m^2/day i.v. on days 1-5 every 4 weeks until complete response or disease worsening/progression was noted. This study is closed to accrual and final analysis is awaited. The ovarian cancer study is ongoing.

Relapsed/refractory AML requiring second salvage was the indication selected for an ongoing phase II trial (NCT00405743, CP4055-106). A preliminary report in June 2009 indicated that 40 patients had been treated with 2000 mg/m^2/day as a continuous i.v. infusion on days 1-5 on a 3-weekly schedule (60). Clinical activity was seen in 6 patients (15%; 4 complete and 2 partial responses). Two responders had refractory disease (first induction after at least 2 regimens), 3 patients were in first relapse with 1 patient having a first remission of < 6 months, and 1 responder was in second relapse with first remission. Median time from start of treatment to remission was 61 days (range: 6-130+) and median overall survival was 88 days (range: 8-292+).

CONCLUSIONS

Cytarabine has had a significant impact on the survival of patients with hematological malignancies. It forms the cornerstone of care for induction therapy in AML patients. Responses to cytarabine-based regimens for this disease vary considerably and are explained in part by drug resistance. Insights into the mediators of cytarabine resistance have allowed for rational drug design and have given rise to the development of new agents like elacytarabine for the treatment of AML patients; while the combination of an anthracycline and cytarabine demonstrates activity, overall cure rates as low as 15% indicate the need for new therapies. The challenge now is to capitalize on the effectiveness of cytarabine while increasing its overall efficacy. By adding the lipid elaidic ester chain, the resulting alternative cell entry mechanism delivers the proven active molecule to cytarabine-resistant cells. To date, at least 320 patients have been treated with this compound. Toxicity has been acceptable and response rates of up to 25% have been reported in phase I/II trials.

SOURCE

Clavis Pharma ASA (NO).

DISCLOSURE

Francis J. Giles has received research funding from Clavis, manufacturer of elacytarabine. R. Swords has received honoraria from Novartis for speaking engagements. The other authors state no relevant conflicts of interest.

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