Pharmacokinetics and Pharmacodynamics of Plasma Clofarabine and Cellular Clofarabine Triphosphate in Patients with Acute Leukemias

Varsha Gandhi,1,2 Hagop Kantarjian,2 Stefan Faderl,2 Peter Bonate,3 Min Du,1 Mary Ayres,1 Mary Beth Rios,2 Michael J. Keating,2 and William Plunkett1,2
Departments of 1 Experimental Therapeutics and 2 Leukemia, The University of Texas M. D. Anderson Cancer Center, Houston, Texas, and 1,2 LEX Oncology, San Antonio, Texas

ABSTRACT
Purpose: The purpose of our study was to investigate the pharmacology of clofarabine and its triphosphate and the pharmacodynamic actions in circulating blasts obtained from acute leukemia patients who entered a Phase I clinical trial of clofarabine.

Experimental Design: Adults with refractory acute leukemias including lymphoblastic (ALL), myelogenous (AML) and chronic myelogenous leukemia in blastic phase (CML-BP) received clofarabine from 4 mg/m2 to 55 mg/m2/day for 5 days as a 1-h i.v. infusion. A total of 26 of the 32 patients were studied for pharmacological investigations.

Results: The maximum tolerated dose was 40 mg/m2/day for 5 days. Plasma pharmacology studies done in 25 patients indicate a linear increase in the plasma clofarabine concentration with increasing doses. At 40 mg/m2, the median plasma clofarabine level was 1.5 μM (range, 0.42–3.2 μM; n = 7). Cellular pharmacokinetic studies done at the end of the first clofarabine infusion in 26 patients appeared dose proportional but showed a wide variation in the concentrations of clofarabine triphosphate. At the maximum tolerated dose, the concentration was a median 19 μM (range, 3–52 μM). In the majority of cases, more than 50% of the analog triphosphate was present at 24 h after infusion. Compared with clofarabine triphosphate concentration, the endogenous level of dATP was low, resulting in a favorable ratio of analog triphosphate:normal deoxynucleoside triphosphate (dNTP) for incorporation into DNA. In association with the accumulation of triphosphate, there was a decrease in DNA synthesis. At 40- and 55-mg/m2 doses, the inhibition of DNA synthesis was maintained to 24 h.

Conclusions: Clofarabine at the maximum tolerated dose was effective with regard to inhibition of DNA synthesis and decline in circulating leukemia blasts. Given the clinical activity of clofarabine in adult acute leukemias, it is of interest to conduct a detailed characterization of the cellular pharmacology of clofarabine triphosphate and its relationship to clinical responses.

INTRODUCTION
As a class of therapeutic agents, nucleoside analogs are more prevalent in the clinical treatment of cancer and viral diseases than other mechanistically similar groups of compounds. Among the medley of these antimetabolites, congeners of deoxyctydine (dCyd) or deoxyadenosine are the most effective agents in clinic. Minor variations in the sugar moiety of the structures have resulted into dCyd analogs with wide variation of clinical application. Cytarabine with an arabinose sugar is the most active drug in acute myeloid leukemia (1). The success of cytarabine generated a flurry of dCyd analogs such as gemcitabine, troxacitabine, and decitabine (2). Although these analogs showed some efficacy in acute leukemias, none were as effective as cytarabine and mostly needed to be used in combinations (3–7).

Purine nucleoside analogs include fludarabine and cladribine, each of which is derivatized with a halogen at the 2-position of the adenine to prevent deamination and, hence, deactivation of the compound (Fig. 1). Although cladribine has been efficacious for pediatric acute leukemias, among adults, both of these deoxyadenosine analogs were ineffective for acute leukemias. However, they have shown different degrees of activity against indolent lymphoproliferative disorders including chronic lymphocytic leukemia, lymphomas, hairy cell leukemia, and Waldenstrom’s macroglobulinemia (8, 9). This may be attributed to the nature of the modifications on their carbohydrates. Fludarabine, an arabinosyl nucleoside, is widely used for chronic lymphocytic leukemia and indolent lymphoma. Cladribine, which has the natural deoxyribose sugar, is the drug of choice for hairy cell leukemia and has proven activity in Waldenström’s macroglobulinemia.

The functional consequence of minor modifications in the structure of these agents provides the rationale for the design and testing of additional nucleoside analogs. Clofarabine (2-chloro-2’-fluoro-2’-deoxy-9-β-D-arabinofuranosyladenine) was synthesized as a rational extension of the deoxyadenosine analog experiences (Fig. 1). This hybrid drug retains the 2-chloroadenine aglycone of cladribine. Reminiscent of fludarabine, clofarabine is further derivatized with a fluorine molecule in the
arabinosyl configuration at the critical 2'-position of the carbohydrate (10). Substitution of a fluorine at C-2', although retaining the arabinose configuration, stabilizes the glycosidic bond, which renders this nucleoside analog highly resistant to bacterial purine nucleoside phosphorylase and to acid hydrolysis (11, 12).

Structure activity relationship investigations demonstrated that clofarabine incorporates the most favorable antimetabolic properties of fludarabine and cladribine. Similar to these purine congeners, clofarabine requires intracellular phosphorylation by dCyd kinase to be metabolized to the triphosphate form necessary for its cytotoxic effect (13). The triphosphate of fludarabine primarily inhibits DNA polymerases, whereas cladribine triphosphate particularly inhibits ribonucleotide reductase. Clofarabine triphosphate has the mechanistically favorable properties of both agents with regard to inhibition of DNA polymerases and ribonucleotide reductase (14–17).

A Phase I clinical trial was conducted in 51 patients with indolent and acute hematological malignancies and in solid tumors to identify the dose-limiting toxicities of clofarabine and to define maximum tolerated doses on a daily-times-5-days schedule (18). Clofarabine, at escalating doses, was administered daily for 5 days as a 1-h i.v. infusion. The dose-limiting toxicity was reached at 2 and 4 mg/m²/day for 5 days in patients with solid tumors and indolent leukemias, respectively. However, the dose was escalated to 55 mg/m² in patients with acute leukemias, before identifying a maximum tolerated level of 40 mg/m². The present report focused on this latter population to detail the plasma pharmacology of clofarabine and the pharmacodynamics of the active triphosphate in leukemia blasts.

PATIENTS AND METHODS

Patients. Adult patients, ≥18 years old with acute leukemia who were not candidates for treatments of higher efficacy or priority were eligible for the study. Informed consent forms, indicating that patients were aware of the investigational nature of this study, were signed according to institutional guidelines. A total of 32 patients were treated, which included 16 adults with acute myeloid leukemia, 13 with acute lymphoblastic leukemia, and 3 with chronic myelogenous leukemia. Of these, 27 consented to participate in laboratory correlative investigations.

Treatment Plan. The Phase I study portion in acute leukemias started at a daily dose of 4 mg/m² infused i.v. by pump over 1 h. The doses were then escalated to 7.5, 11.25, 15, 22.5, 30, 40, and 55 mg/m²/day. Because dose-limiting toxicities were observed at 55 mg/m², additional patients were treated at 40 mg/m² to define the maximum tolerated dose (18).

Drug and Other Chemicals. Clofarabine for clinical use was initially prepared by Ash Stevens Inc, Detroit, MI and formulated for injection by the National Cancer Institute, Bethesda, MD). Authentic clofarabine standard was used for assay validation, and for identification and quantitation of the nucleoside in plasma. The assay has a sensitivity range from 10 to 5000 ng/mL.

Cellular Pharmacology. Cell pellets from blood samples were diluted with PBS, and mononuclear cells were isolated using Ficoll-Hypaque density-gradient step-gradient centrifugation procedures described previously (21). A Coulter electronics channelizer (Coulter Corporation, Hialeah, FL) was used to determine the mean cell volume. After being washed with PBS, cells were processed for nucleotide extraction. Normal nucleotides and clofarabine triphosphate were extracted from cells using standard procedures with HClO₄. Triphosphates were separated on an anion-exchange Partisil-10 SAX column (Waters Corporation, Milford, MA) using high-pressure liquid chromatography as described in detail previously (21). The intracellular concentration was calculated and expressed as the quantity of nucleotides contained in the extract from a given number of
cells of a determined mean volume. This calculation assumes that nucleotides are uniformly distributed in total cell water. In general, the lower limit of quantitation of this assay was about 1 pmol in an extract of 2 × 10^7 cells, corresponding to a cellular concentration of ~0.2 μM. For many samples, extract from as many as 8 × 10^7 cell-equivalents were analyzed to detect the peak.

**Cellular Pharmacodynamics of Deoxynucleotides.** To determine the effect of clofarabine on the cellular deoxynucleoside triphosphate (dNTP) pool, leukemia cells were extracted with 60% methanol for the determination of dNTPs. The DNA polymerase assay as modified by Sherman and Fyfe (22) was used to quantitate dNTPs in the cell extracts. Klenow fragment of DNA polymerase I lacking exonuclease activity (United States Biochemical Corporation, Cleveland, OH) was used to start the reaction. The assay mixture contained 100 mM HEPES buffer (pH 7.3), 10 mM MgCl₂, 7.5 μg BSA, synthetic oligonucleotides of defined sequences as templates annealed to a primer, [³H]dATP or [³H]dTTP, and either standard dNTP or the extract from 1 or 2 × 10⁶ leukemia cells isolated before or after therapy. Reactants were incubated for 1 h and were applied to filter discs; after they were washed, the radioactivity on the discs was determined by liquid scintillation counting and was compared with that in the standard dNTP samples. The concentrations of dNTPs in leukemia cells were calculated assuming uniform distribution in total cell volume.

**Cellular Pharmacodynamics of DNA Synthesis.** Cells obtained from blood samples were diluted with PBS and suspended in RPMI 1640 with 10% fetal bovine serum. The cells were incubated with [³H]thymidine (1 μCi/ml) for 30 min in a multi-screen assay system (Millipore Corp., Bedford, MA). The cells were then collected on multi-screen-GV filters under vacuum and were washed four times each, with ice-cold perchloric acid, water, and 100% ethanol. The radioactivity in the acid-insoluble material retained on the filters was measured by scintillation counting, and the results were expressed as percentage of control value from cells obtained before therapy.

**Calculations and Statistical Analyses.** Linear regression for plasma clofarabine levels and nonlinear regression analyses for r and rectangular hyperbola curves for clofarabine triphosphate accumulation were obtained using the Prism software program (GraphPad Software, Inc., San Diego, CA).

**RESULTS**

**Plasma Pharmacology.** Similar to other nucleoside analogs, the peak level of clofarabine in plasma occurred at the end of the infusion. Although at each dose there was heterogeneity among patients regarding the plasma concentration of clofarabine, there appeared to be dose-proportional increase in the plasma clofarabine concentration with the doses administered (Fig. 2). Linearity was also evident when the data were analyzed by linear regression (r² = 0.65; n = 24). At 40 mg/m², the maximum tolerated dose for acute leukemia, the median plasma clofarabine level was 1.5 μM (range, 0.42 to 3.2 μM; n = 7). However, at this dose, it is also clear that there is substantial variation in the plasma concentration of clofarabine at a given dose.

**Cellular Pharmacology.** Levels of clofarabine triphosphate were analyzed at the end of clofarabine infusion in the circulating leukemia blasts of 26 patients. There was a wide variation regarding the intracellular concentration of clofarabine triphosphate that was more apparent at higher doses (≥30 mg/m²; Fig. 3A). At doses between 4 and 22.5 mg/m², there appeared to be a dose-dependent accumulation of triphosphate in the leukemia blasts of these patients. However, there seemed to be loss of proportionality at doses of ≥30 mg/m²/day (Fig. 3A). At the maximum tolerated dose, the median cellular clofarabine triphosphate concentration was 19 μM (range, 3–52 μM). On the other hand, at 55 mg/m²/day, the cellular levels of clofarabine triphosphate varied between 6 and 23 μM. To better define the relationship between the concentration of the parent nucleoside analog in plasma and that of its active triphosphate in circulating blasts, we evaluated the actual concentration of these two compounds at the end of the infusion in each patient (Fig. 3B). The plasma clofarabine concentration varied between 0.18 and 6.17 μM. With this range of concentrations, there seemed to be a saturation in the accumulation of clofarabine triphosphate by blasts in the range of 1 to 1.5 μM plasma clofarabine. Because these levels of clofarabine are achieved at doses of 30 and 40 mg/m²/day infused over 1 h, maximal triphosphate accumulation would be expected at the maximum tolerated dose.

To determine the pharmacokinetic characteristics of clofarabine triphosphate in leukemia blasts and whether there were differences in blasts from myeloid or lymphoid origin, data were compared in these two populations (Fig. 4). Comparison of clofarabine triphosphate concentrations at the end of infusion in these two cell lineages (Fig. 4). Comparison of clofarabine triphosphate concentrations at the end of infusion in these two cell lineages, indicated that there is heterogeneity among each group. Similar variations were also observed at 24 h after infusion. The ratio of clofarabine triphosphate concentration at the end of infusion compared with that at 24 h was a
median 0.57 (range, 0.05 to 0.92; \( n = 9 \)) in lymphoid blasts and 0.52 (range, 0.08–1.00; \( n = 12 \)) in myeloid blasts. Intrapatient analysis of the triphosphate concentrations demonstrated that 15 of the 21 paired samples (6 of 12 lymphoid; 9 of 12 myeloid) had retained more than one-half of the initial triphosphate level at 24 h. Taken together, these results suggest similar cellular pharmacokinetics of clofarabine triphosphate in lymphoid and myeloid lineages.

Cellular Pharmacodynamics of DNA Synthesis. To determine whether, in association with the maximum accumulation of clofarabine triphosphate at the maximum tolerated dose, there was a dose-dependent inhibition of DNA replication, we analyzed DNA synthetic capacity of blasts at pretreatment and compared the capacities at the end of infusion for 3 to 4 days of therapy. Representative patient data are shown for 22.5, 30, and 55 mg/m\(^2\)/day (Fig. 5). At 22.5 mg/m\(^2\)/day, there was a 60% decrease in DNA synthesis after the end of infusion (eoi) of clofarabine. This was followed by a partial recovery of DNA synthesis before the second administration of clofarabine. The increase in DNA synthesis was further affected after every infusion; however, there was a partial recovery. At 30 mg/m\(^2\)/day, the blasts from this patient had an almost complete inhibition of DNA synthesis after the end of clofarabine infusion. As with the lower dose, the inhibition of DNA synthesis was not sustained. At the 55 mg/m\(^2\)/day dosage of clofarabine, the inhibition of DNA synthesis was almost complete after the end of infusion, remained inhibited at 4 h after infusion, and was sustained until the next administration of clofarabine. These data suggest a dose-dependent effect on the maintenance of DNA synthesis inhibition in the blasts during therapy with clofarabine.

The dose responsiveness of duration of DNA synthesis inhibition was evident after samples from 12 patients were evaluated (Fig. 6). At the end of infusion, at 22.5 mg/m\(^2\)/day, there was a 75% decline in DNA synthesis, which seemed to be dose-dependent with a >90% inhibition at 55 mg/m\(^2\). At 24 h, the recovery of DNA synthesis was evident at 22.5- and 30-mg/m\(^2\) doses; however, the DNA synthetic capacity remained inhibited in samples from patients who received the 40- and 55-mg/m\(^2\)/day doses.

Cellular Pharmacodynamics. The presence of clofarabine triphosphate with an associated inhibition of DNA synthesis should result in a decline in the circulating leukemia cells. To determine this cellular pharmacodynamic effect, WBCs in peripheral blood were counted before treatment and after 5 days of

Fig. 4 Dose- and diagnosis-dependent accumulation of clofarabine triphosphate in blasts from patients with acute lymphoblastic leukemia (A), or acute myeloid leukemia and chronic myelogenous leukemia in blastic phase (B). Blood samples were obtained at the end of clofarabine infusion and at 24 h after infusion. The doses of clofarabine were 4 (○), 7.5 (△), 11.25 (●), 15 (○), 20/22.5 (●), 30 (○), 40 (●), and 55 (□) mg/m\(^2\). The patients with chronic myelogenous leukemia in blastic phase (+) in B received 15, 22.5 (two patients), or 55 mg/m\(^2\) of clofarabine. The clofarabine triphosphate concentration was quantitated as described in the “Patients and Methods” section. Triphosphate concentrations were not obtained at 24 h in three patients. Cl-F-ara-ATP, clofarabine 5’-triphosphate.
therapy. For 12 patients entered at the maximum tolerated dose of 40 mg/m²/day, the WBC count at the start of therapy ranged from $1 \times 10^3$ to $78 \times 10^3 / \mu l$ in peripheral blood with a blast percentage of 80–97%. After 5 days of therapy, there was a consistent cytoreduction in the WBC count in all of the peripheral blood of these patients with a median decline of 97% (range, 68–99%).

**Cellular Pharmacodynamics of Deoxynucleotides.** The decline in WBCs at low levels of clofarabine triphosphate indicated the potency of clofarabine. Additionally, the ratio of clofarabine triphosphate:dATP may be favorable for the intracellular actions of clofarabine. Enough leukemia blasts were obtained from nine patients to quantitate endogenous dATP pools at the start of therapy. The median concentration of dATP was 1.8 μM (range, 0.4–22 μM; n = 9). Furthermore, the dATP concentration declined further (45, 50, and 70% decrease; data not shown) in the circulating leukemia blasts from three of five patients after clofarabine infusion, whereas in two, it remained unchanged.

**DISCUSSION**

The accumulation of clofarabine in plasma was dose proportional at the end of the 1-h i.v. infusion (Fig. 2). The clofarabine concentration projected at the end of the infusion of the maximum tolerated doses (40 mg/m²/day) was ~2 μM. This level was well above the toxic level for leukemia cell lines growing in culture (14, 16). In contrast to the plasma pharmacology of the parent nucleoside, the dose-response for accumulation of the active triphosphate in leukemia cells appeared to deviate from linearity at clofarabine dose rates greater than 30 mg/m² infused over 1 h (Fig. 3A). Furthermore, this was related to the clofarabine concentration in plasma at the end of the infusion (Fig. 3B). Investigations with cytarabine (23) and gemcitabine (24) demonstrated a dose-rate dependency for the accumulation of the respective triphosphates in leukemia blasts and mononuclear cells (25–27) that was related to the concentration of the respective nucleoside in plasma. An understanding of the plasma concentration that maximizes the rate of triphosphate accumulation has been the basis for adjusting infusion rates to target the optimum plasma levels of nucleosides in prospective trials (3, 28–30). The saturation in the rates of triphosphate accumulation in cells has been explained by investigations of the kinetic mechanism of dCyd kinase (31), which catalyzes the initial phosphorylation of these nucleosides and of clofarabine. However, although dCyd kinase is the rate-limiting step in the accumulation of the triphosphates of cytarabine and gemcitabine, clofarabine triphosphate accumulation appears to be limited by the rate of phosphorylation of the monophosphate (16, 32). This is also the case with cladribine (33), which, as with clofarabine, has the 2-chloro-adenine aglycone (Fig. 1). Furthermore, the $K_m$ of dCyd kinase for clofarabine is 14 μM,
which indicates that at or around 2 μM plasma clofarabine, the dCyd kinase would not be saturated (13). Hence, the apparent lessenning of the rate of clofarabine triphosphate accumulation at 2 μM clofarabine in plasma may reflect the rate of monophosphate conversion to the diphosphate. Additional investigations are needed to fully understand the kinetic basis for the apparent concentration dependence of clofarabine triphosphate accumulation.

Heterogeneity among individuals is a common feature with regard to the accumulation of nucleoside analog triphosphates, and clofarabine does not appear to be an exception (Fig. 3). Although it is not possible to critically evaluate dose response relationships in the context of leukemia biology or clinical response because too few individuals received the same clofarabine dose in this Phase I trial, consideration of the relative ability of blasts to retain clofarabine triphosphate can be accomplished in 21 of the patients (Fig. 4). Comparison of the triphosphate concentration in each patient at the end of the infusion relative to that present at 24 h can be taken as an indication of drug retention. Calculation of this ratio indicates little difference between lymphoid (Fig. 4A) and myeloid cell types (Fig. 4B) with 6 of 9 lymphoid and 9 of 12 myeloid samples exhibited prolonged retention of the triphosphate, i.e., t1/2 >24 h. The presence of significant concentrations of clofarabine triphosphate before the second infusion provides the potential for incremental increases in the levels of the active metabolite during subsequent infusions in the 5-dose course of therapy.

The finding that the blasts from many of the patients with acute leukemia retain more than one-half of the initial concentration of clofarabine triphosphate for 24 h is in contrast to the ability of blasts for similar patient populations to retain the triphosphates of other deoxyadenosine analogs. For instance, the triphosphates of purine nucleoside analogs fludarabine (mean t1/2 ~8 h; Refs. 34, 35) and cladribine (mean t1/2 ~10 h) are all eliminated more rapidly from acute leukemia blasts than was clofarabine triphosphate. Clofarabine also differs from these other purine nucleoside analogs in that it is clinically active in adult acute leukemias as a single drug at tolerable doses. Although the relatively small sample size precludes firm conclusions, the slow elimination of clofarabine triphosphate is reminiscent of that observed for nelarabine triphosphate in chronic lymphocytic leukemia lymphocytes and T lymphoblasts obtained from patients with T-acute lymphoblastic leukemia (36, 37). In these samples, there was a strong correlation between clinical response and the cellular concentration of nelarabine triphosphate.

The mechanistic investigations with clofarabine have demonstrated that this deoxyadenosine analog has dual actions on the inhibition of DNA synthesis: (a) by direct incorporation into DNA followed by the inhibition of further DNA chain elongation by DNA polymerases; and (b) by the inhibition of ribonucleotide reductase, the enzyme responsible for the supply of dNTP pool needed for replicative DNA synthesis (14, 16, 17). The ratio of the concentration of clofarabine triphosphate to the dATP pool would be a primary determinant for analog incorporation into DNA. Data from nine patients samples studied during the present investigation suggest that the intracellular concentration of dATP is relatively low (median, 1.8 μM). Furthermore, after clofarabine infusion, in the circulating leukemia blasts of some patients, this level declined even more. Hence, it would be predicted that the clofarabine triphosphate concentrations achieved in the leukemia blasts after the first infusion of clofarabine (median of 19 μM at the maximum tolerated dose) should provide a ratio of clofarabine triphosphate to the triphosphate of the normal dNTP that favors the incorporation of the deoxyadenosine analog into DNA, which would result in the inhibition of DNA synthesis.

The dose-dependent pharmacodynamics of clofarabine triphosphate were evident with regard to the duration of DNA synthesis inhibition in blasts after a single clofarabine infusion (Fig. 6). Although doses between 22.5 and 55 mg/m2 reduced DNA synthesis by 75–95%, this nearly recovered to pretreatment levels in blasts from patients who received 22.5 and 30 mg/m2 of clofarabine. In contrast, DNA synthesis remained suppressed at 24 h in the blasts of patients treated with 40 and 55 mg/m2. As with other nucleoside analogs (38, 39, 3), it is likely that the timing of recovery of DNA synthesis is related to the cellular concentration of triphosphate and its rate of elimination. The extent and duration of the inhibition of DNA synthesis is strongly associated with clofarabine killing of cells in culture (16, 17). Consistent with the observations in the cell line model systems, data regarding clofarabine-mediated cytoxicity at the maximum tolerated dose suggests that, in all patients, this dose was effective for this pharmacodynamic end point. Because the inhibition of DNA synthesis and its effect on leukemia cells is related to the clinical response to other nucleoside analogs (39), it is important to develop a thorough understanding of this relationship to facilitate the design of optimal schedules and combinations with clofarabine.

Cytarabine is the agent with which other nucleoside analogs are compared in the therapy of acute leukemias. Although greater concentrations of cytarabine triphosphate are accumulated in leukemic blasts than are concentrations of clofarabine triphosphate, the cytarabine metabolite is rapidly eliminated with a half-life of 2–3 h (38, 39). The ability of leukemia blasts to retain cytarabine triphosphate is related to its pharmacodynamic action on DNA synthesis and has been used as a basis for determining the schedule of administration of the parent nucleoside with a view to sustaining inhibition (38). Although blasts accumulate clofarabine triphosphate to lesser concentrations, it is clear that DNA synthesis inhibition is prolonged at the maximum tolerated dose. Furthermore, the slow elimination rates suggest that the triphosphate that remains before the second dose will be augmented by subsequent clofarabine doses on this schedule. Given the clinical activity of clofarabine in adult acute leukemias (18, 40, 41), it is of interest to characterize the cellular pharmacology of its triphosphate in leukemia blasts during Phase II clinical investigations, and to seek correlations between its pharmacodynamic profile and clinical response (40). Additionally, the impact of this agent on normal bone marrow stem progenitor cells needs to be evaluated. An understanding of the pharmacokinetics and pharmacodynamics of the active triphosphate in leukemia and normal progenitor cells may provide a basis for optimizing the schedule of clofarabine administration.
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