Evaluation of the in Vivo Antitumor Activity and In Vitro Cytotoxic Properties of Auranofin, a Coordinated Gold Compound, in Murine Tumor Models

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ABSTRACT

The coordinated gold compound, 2,3,4,6-tetra-O-acetyl-1-thio-beta-d-glucopyranosato-S-triethylphosphine gold (auranofin; Ridaura), was evaluated for antitumor activity in a variety of mouse tumor models. Of the 15 tumor models evaluated, auranofin was found to be active only against i.p. P388 leukemia. A number of dose schedules were used to measure activity against P388 with optimal activity observed at 12 mg/kg given daily, i.p., on Days 1 to 5. Auranofin was active against i.p. P388 leukemia only when administered i.p.; the drug was completely inactive when administered i.v., s.c., or p.o. on Days 1 to 5.

Evaluation of the effects of auranofin in vitro demonstrated that (a) survival curves for B16 melanoma cells as measured by the clonogenic and dye exclusion assays were exponential and monophasic; (b) cell cycle distribution was not altered, and auranofin displayed no preferential cytotoxicity to logarithmic or plateau growth phase cell populations; (c) auranofin inhibited DNA, RNA, and protein synthesis at cytotoxic concentrations but showed no selective effect; (d) the cytotoxic activity and cellular association of gold from auranofin were dose, time, and temperature dependent; and (e) binding of auranofin to serum proteins markedly decreased cellular uptake of gold and cytotoxicity of auranofin in vitro.

INTRODUCTION

Auranofin [2,3,4,6-tetra-O-acetyl-1-thio-beta-d-glucopyranosato-S-triethylphosphine gold(II); Ridaura SKF D-39162] is a p.o.-absorbed gold complex shown to be active in the treatment of rheumatoid arthritis (3, 22). This drug has been shown to inhibit human lymphocyte responsiveness both in vivo (7, 24) and in vitro (5). More recently, there have been a number of reports on the in vivo antiproliferative effects of auranofin on a variety of animal and human tumor cell lines in vitro (4, 11, 12, 20). Auranofin has also demonstrated potent cytotoxic activity in the human primary tumor clonogenic assay against a variety of human tumor types.2 In vivo antitumor activity has also been reported for auranofin against P388 mouse leukemia (21).

To better define the potential antitumor activity of auranofin, we have studied its effects in a variety of in vitro and in vivo systems (4, 11). In this paper, we describe the evaluation of antitumor activity of auranofin in a panel of mouse tumor models and present the results of in vitro studies which were designed to evaluate the possible mechanisms of the cytotoxic activity of the drug.

MATERIALS AND METHODS

Evaluation in i.p. P388 Leukemia

P388 leukemia cells (106), maintained by serial transplantation in syngeneic DBA/2 mice, were inoculated i.p. in C57BL/6 x DBA/2 F1 (hereafter called B6D2F1) mice. Twenty-four hr later, if the tumor inoculum proved to be free of bacterial contamination (as determined by 24-hr incubation in thioglycollate broth), animals were randomized into groups of 6 and housed in shoe box cages. Auranofin was dissolved in 95% ethanol. A 0.9% NaCl solution was added in sufficient quantity such that the desired dose was delivered in 0.5 ml. The final concentration of ethanol was 10%. Dilutions for lower doses were made with 0.9% NaCl solution so that there was a decreasing proportion of organic solvent in the vehicle with decreasing dosage. Formulations were prepared immediately prior to injection. (The drug was diluted and formulated in the same manner for evaluation in each of the tumor systems described.) Auranofin was administered i.p. on Days 1 through 5 (i.e., treatment was initiated 24 hr after tumor inoculation). Each experiment includes 3 groups of 6 animals as untreated controls and animals treated with a positive control, cis-diamminedichloroplatinum(II) (cisplatin) (Sigma Chemical Co., St. Louis, MO), at 2 dose levels. Each experiment also included an inoculum titration consisting of groups of 8 mice inoculated i.p. with 106 to 108 P388 leukemia cells. The titration was used to calculate cell kill achieved by treatment with drugs (16). The equation used for calculation of net change in log tumor cell burden at the end of therapy is [(x - b)/m] - y, where x is the median survival time in days following cessation of therapy, b is the median time to death following inoculation of one cell of P388, and m is the slope of the inoculum-survival time curve. These latter 2 factors were determined by regression analysis of titration data excluding long-term survivors. The value of y is the tumor cell burden present at the start of therapy calculated as 6 + log 10[6], where 6 is the original inoculum (106 cells), and DT7, the cell population doubling time, is -m log 2.

Other in Vivo Tumor Models

Other murine tumor models were maintained by serial transplantation in syngeneic mice and were implanted i.p. and/or s.c. for evaluation of auranofin. Tumor models included: M5076 reticulum cell sarcoma, B16 melanoma, and Lewis lung carcinoma (maintained in C57BL/6 mice and evaluated in B6D2F1 mice); Madison 109 lung carcinoma and colon carcinoma 26 (maintained and evaluated in BALB/c mice); and mammary adenocarcinomas 15/c and 13/c (maintained and evaluated in C3H mice). All tumors were obtained from the National Cancer Institute tumor bank at Frederick Cancer Research Center, Frederick, MD.

For evaluation in the slower-growing solid tumor models, auranofin, formulated as described above, was administered i.p. daily for 10 days beginning 1 day after tumor implantation. The drug was administered in each tumor model at 5 logarithmically spaced dosage levels which encompassed the maximally tolerated dose. Activity was assessed by inhibition of tumor growth at the site of implant for s.c. tumors and prolongation of median life span for i.p. and s.c. tumors. Tumor volume was determined when tumors in untreated control mice averaged about 1000 cu mm (2 to 3 weeks after inoculation). Tumor volume was

1To whom requests for reprints should be addressed.
2D. Von Hoff and C. K. Mirabelli, unpublished results.

Received July 26, 1984; accepted October 9, 1984.
estimated by measurement of perpendicular diameters with vernier calipers using the equation of 0.5 x length x (width)^2.

**Cell Culture Techniques**

B16 melanoma cells (highly metastatic subline, F10) (14) were maintained as monolayer cultures in MEM* (Grand Island Biological Co., Grand Island, NY) supplemented with 10% calf serum and 1% penicillin-streptomycin in a 5% CO₂-humidified incubator at 37°.

In **Vitro Cytotoxicity Assays**

**Monolayer Clonogenic Assay.** Asynchronous populations of cells were harvested and replated at 5000 cells/plate in sterile 60 x 15-mm Petri plates. Plates were incubated overnight to allow attachment of cells to the plate surface. Cells were treated with auranofin for 2 hr in either the presence or absence of 10% FCS (as indicated) in MEM under sterile conditions followed by aspiration of medium. Plates were washed one time with 5 ml of PBS, followed by addition of 5 ml of fresh medium. Plates were incubated for 5 days at 37° in a CO₂ incubator. Viability was measured by the ability of a cell to form a colony greater than 50 cells. Colonies were fixed with 0.5% crystal violet in 95% ethanol. Plates were dried and counted with a Biotron III automatic cell counter (New Brunswick Scientific Co., Edison, NJ). The mean ± S.D. of triplicate samples was determined for each drug concentration. The data were analyzed by plotting the log of the survival fraction (number of colonies in drug-treated plates/number of colonies in controls) versus the drug concentration.

**Cell Cycle Analysis.** The effects of auranofin on cell cycle progression of logarithmically growing B16 melanoma cells were analyzed by measurements of relative DNA content of individual cells. Cells were fixed with ethanol, stained with methylene blue, and analyzed using a fluorescence-activated cell sorter (Coulter Electronics, Inc., Hialeah, FL) as described previously (18).

Logarithmic and plateau growth phases were obtained by harvesting confluent monolayers of B16 cells and replating at 7.5 x 10^5 cells/plate. Cells were then incubated at 37° in 5% CO₂, and the number of cells/plate was monitored for each group of plates. The plates with an initial concentration of 7.5 x 10^5 cells/plate reached a plateau at a concentration of 4 x 10^6 cells/plate at 50 hr through 90 hr, whereas the cells plated at 1 x 10^6 cells/plate were in exponential growth phase from 20 hr through 90 hr. Thus, exponentially growing cells were selected from plates initially plated at 1 x 10^6 cells/plate and treated with auranofin at 70 hr after plating, whereas plateau-phase cells were represented by those cells in plates which were initially plated at 7.5 x 10^5 cells/plate and treated with auranofin at 70 hr postplating. Following 2 hr of drug incubation, the cells were harvested with trypsin, counted, and replated at 5000 cells/plate, and the percentage of survival was determined.

**Inhibition of Macromolecular Synthesis.** Logarithmically growing cells were harvested at time intervals of 1.5 x 10^6 cells/ml. One hundred µl of a drug-containing medium were added to 900 µl of cell suspension. The cell suspensions were incubated at 37° for 1 hr with continuous shaking. [3H]Leucine (3 µCi/ml), [3H]thymidine (1 µCi/ml), or [3H]uridine (1 µCi/ml) was then added, and incubations were continued for 2 hr. Immediately after incubation, the cell suspensions were added to scintillation vials and treated with auranofin (195Au labeled, 31.9 µCi/mmol) was added to medium containing FCS (5% v/v). The 195Au in the medium was measured by y counting. Protein-associated 195Au in the medium was determined in a Beckman Gamma 8000 counter (Beckman Instruments, Irvine, CA).

**RESULTS**

**In Vivo Antitumor Activity of Auranofin.** The activity of auranofin against i.p. P388 leukemia is shown in Chart 1. The dose response presented is a composite of 30 experiments with auranofin administered i.p. on Days 1 through 5 following i.p.

In **Vital Dye Exclusion.** Logarithmically growing cells were harvested with versene and resuspended in fresh medium at 10^6 cells/ml. One-half ml of medium containing auranofin (195Au labeled, 31.9 µCi/mmol) was added to 0.5 ml of culture medium. Following incubation under the conditions specified in "Results," the cells were transferred to glass microfiber filters in a sampling manifold and were then washed 5 times with cold PBS. Filters were then dried and counted with a Biotran III automatic cell counter (Beckman Instruments, Irvine, CA).

**Extraction of Non-Protein-associated Gold from Medium.** Two µl (7.7 x 10^6 dpm) auranofin (195Au) were added to medium containing FCS at concentrations between 0 and 10%. Following 5 min of incubation at 0°C, 100 µl of the mixtures were then added to 400 µl of toluene in microfuge tubes. The toluene was removed, and the aqueous layer was again extracted with 400 µl of toluene. The 2 toluene extracts were pooled, and the 195Au in both the toluene and medium was measured by y counting. Protein-associated gold is not extracted into the toluene.

**The abbreviations used are:** MEM, minimal essential medium; PBS, phosphate-buffered saline; TCA, trichloroacetic acid; FCS, fetal calf serum; ILS, increase(d) life span; MTD, maximum tolerated dose; IC50, drug concentration required to reduce cell survival by 50% on the exponential part of the survival curve.

*J. Dent, personal communication.

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tumor implantation. The optimal dose of auranofin, 12 mg/kg, produced an average of 59% ILS. Reduction of the dose to 6 mg/kg resulted in an average of 51% ILS. Cisplatin was included as a positive control in these experiments and produced an average of 117% ILS at the optimal dose of 2 mg/kg.

Table 1 shows the results of experiments in which the schedule dependency of auranofin in the treatment of i.p. P388 leukemia was evaluated. The results of the first experiment indicate that auranofin is slightly more effective administered daily than when given at a 2-day interval and is significantly less effective when given on the every fourth day schedule. This may be a reflection of the fact that the maximally tolerated dose is not increased by lengthening the interval between doses. The effects of increasing the number of injections per day on both the potency and activity of auranofin were determined (Table 1, Experiment 2), since administration of auranofin twice daily had been shown by Simon et al. (21) to be more effective than daily treatment. The results of these experiments indicate that increasing the number of injections per day decreased the MTD per injection with a similar total daily MTD. In contrast to the results presented by Simon et al. (21), the maximum ILS achieved on the split-dose schedules was essentially identical to results achieved with single daily doses. Conversion of the dose-response data from Experiment 2 to cell kill is shown in Chart 2, which shows that decreasing interval between treatments at each of the doses tested produced a decreased in the amount of cell kill achieved. For example, treatment of the tumor with 2 mg/kg once a day for 5 days produced a log net cell kill of 0.33 with each treatment, whereas treatment with 2 mg/kg 2, 4, and 8 times per day achieved net log cell kills of 0.17, 0.09, and 0.06, respectively.

The antitumor activity of auranofin was also evaluated in a variety of mouse solid tumor model systems. These included M5076 reticulum cell sarcoma (implanted i.p. or s.c.), B16 melanoma (implanted i.p. or s.c.), Madison 109 lung carcinoma (implanted i.p. or s.c.), colon carcinoma 26 (implanted i.p. or s.c.), Lewis lung carcinoma (implanted i.p. or s.c.), and mammary adenocarcinomas 16/c and 13/c (implanted s.c.). Auranofin was administered i.p. In each of the above tumor models, auranofin neither prolonged life span nor inhibited the growth of s.c.-implanted tumors. Auranofin was also evaluated in mice bearing i.v. P388 leukemia, and the drug was inactive when administered i.p., i.v., or s.c.

As shown in Table 2, the activity of auranofin against i.p. P388 leukemia is evident only when the drug is administered i.p. Auranofin, given i.v., s.c., or p.o., was essentially inactive in P388 leukemia regardless of dose level.

**Effects of Auranofin on Tumor Cells in Vitro.** The ability of auranofin to inhibit the growth of cells in vitro has been reported by several investigators (1, 5, 20). We have reported previously that auranofin is as cytotoxic or more cytotoxic to a number of tumor cell lines in vitro as a number of clinically used antitumor agents (11). The following studies were performed to better define the mechanism(s) by which this drug inhibits the growth of cells in vitro.

The effect of auranofin on the clonogenic capacity of B16 melanoma cells following a 2-hr treatment is shown in Chart 3A. The survival curve was monophasic and exponential. The cytotoxic potency of auranofin against P388 leukemia and B16 melanoma cells was equivalent as determined in the clonogenic assay with the cells grown in soft agar (data not shown). Chart 3B shows that the cytotoxic effect of auranofin on B16 cells was also dependent on the duration of treatment. Unlike the effects of varying concentrations, the survival curves generated in the time course studies were biphasic with a more rapid rate of cell kill through 2 hr, followed by a less rapid rate through the next 22 hr.

The ability of B16 melanoma cells to exclude trypan blue as a function of auranofin treatment was evaluated and compared to clonogenicity (Chart 4). The response to auranofin treatment as measured by both end points was exponential and monophasic. Although the slopes of the survival curves appeared to differ,
 Chart 3. Cytotoxic activity of auranofin against B16 melanoma cells as measured in the monolayer clonogenic assay. A, colony formation as a function of auranofin concentration following a 2-hr exposure to drug in the presence (•) and absence (○) of 10% FCS; B, colony formation as a function of the exposure time of cells to auranofin at 1 (•) and 4 μM (○). Points, mean of 3 assays; bars, S.E.

 Chart 4. Cytotoxicity of auranofin against B16 cells following a 2-hr exposure to the drug and measured by the monolayer clonogenic assay (○) and the vital dye exclusion assay (●). Points, mean of 3 assays; bars, S.E.

 Chart 5. Effects of auranofin treatment on the ability of B16 cells to exclude trypan blue. Cells were incubated with auranofin for 2 hr at 37° (○) and 0° (●), and their ability to exclude trypan blue was then measured.

the IC₅₀ values were not significantly different. The effect of auranofin on cell viability measured by trypan blue exclusion was found to be temperature dependent. As described in Chart 5, the IC₅₀ following 2-hr exposure at 37° was 15-fold lower than that at 0°.

Cell Cycle Analysis. Flow cytometric analysis of B16 melanoma cells treated with auranofin indicated no drug-induced progression delay; treatment of the cells with auranofin (0.0125 μM) for 24 hr allowed for greater than 90% cell survival and produced no changes from the control pattern (no drug) in the DNA distribution histograms. At concentrations of auranofin above 0.2 μM, extensive cell lysis occurred with debris accumulating in the lower channels of the histograms, but the overall distribution of cells in the G₁, S, and G₂-M compartments was not altered significantly from untreated populations (data not shown).

To determine whether auranofin showed any selective cyto-
toxicity towards cycling versus noncycling cells, both logarithmic and plateau phase populations of B16 cells were prepared and treated with drug for 2 hr at 37°, and their clonogenic capacity was determined. The resulting survival curves were both exponential with equivalent IC₅₀ values (stationary cell population, 6.5 ± 1.0 μM; logarithmic cell population, 7.0 ± 0.8 μM).

**Effect on the Incorporation of ³H-labeled Precursors into DNA, RNA, and Protein.** The effects of auranofin on the incorporation of ³H-labeled precursors into DNA, RNA, and protein were compared with those of 3 known specific inhibitors of macromolecular syntheses (Table 3). Auranofin inhibited the uptake of all 3 precursors into TCA-insoluble materials. However, unlike the 3 standard agents, auranofin showed no significant preferential inhibitory effect on either DNA, RNA, or protein synthesis. Although auranofin appeared to inhibit DNA synthesis at the lowest concentration, the IC₅₀ values for the inhibition of synthesis of the various macromolecules were similar to those which rendered the cells permeable to trypan blue under similar experimental conditions (Chart 4).

**Association of Gold from Auranofin with B16 Melanoma Cells.** The association of auranofin-derived gold with cells in vitro was measured using ¹⁹⁵Au-labeled auranofin in a filter binding assay as described in "Materials and Methods." Under conditions identical to those used in the cytotoxicity studies shown in Chart 4 (i.e., 2-hr incubation; 37°, 10% FCS; and 5 × 10⁵ cells), the cellular association of ¹⁹⁵Au was linearly proportional to the auranofin concentration with no evidence of saturation up to 20 μM auranofin (Chart 6A). At cytotoxic IC₅₀ concentrations measured by the clonogenic assay, the IC₅₀ values for the inhibition of synthesis of the various macromolecules were similar to those which rendered the cells permeable to trypan blue under similar experimental conditions (Chart 4).

**Table 3**

<table>
<thead>
<tr>
<th>Compound</th>
<th>IC₅₀ (μM) for precursor uptake into TCA-precipitable material</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>[³H]Thymidine</td>
</tr>
<tr>
<td>Aphidicolin</td>
<td>0.3 ± 0.03</td>
</tr>
<tr>
<td>Acitretin D</td>
<td>6 ± 0.6</td>
</tr>
<tr>
<td>Azetocysitoxanminide</td>
<td>0.09 ± 0.01</td>
</tr>
<tr>
<td>Auranofin</td>
<td>6 ± 0.4</td>
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</table>

* Mean ± S.E.

**DISCUSSION**

In a previous study, Simon et al. (21) reported that auranofin was effective in increasing the life span of mice inoculated with lymphocytic leukemia P388. In their study, auranofin was administered i.p. every fourth day, daily, and twice per day for a 9-day course of treatment. The drug was least effective given every fourth day (40% ILS) and most effective given twice per day (120% ILS). In our studies, auranofin was less effective against P388 leukemia, and we did not find that multiple daily treatment resulted in increased antitumor activity. The multiple dosing experiments shown in Table 1 indicate that dosage fractionation does not permit the administration of a higher total daily dose of auranofin nor does it result in an improvement in the antitumor activity of the drug.

Although auranofin appears to kill cells in vitro in a log-linear fashion with respect to concentration (first-order cell kill, Chart 2), there is a definite plateau in the cell kill curve determined from in vivo experiments (Chart 1). On the daily treatment schedule, the maximum cell kill achieved is about 0.6 log at 8 mg/kg. There is no increase in cell kill at 16 mg/kg, even though this dose is well tolerated by mice. Another characteristic of the cell kill kinetics of auranofin in vivo is the decrease in cell kill at any particular dose level with shorter intervals between doses of the drug. Although speculative at present, this could be due to a time-dependent tolerance (tachyphylaxis) induced by auranofin in surviving cells [e.g., induction of metallothionein (13, 17)] or, based on studies with serum in vitro, a transient enhancement of albumin levels in peritoneal fluid induced by auranofin treatment.
Our studies included an extensive evaluation of the antitumor activity of auranofin in a spectrum of mouse tumor models. Of these, only i.p. P388 leukemia responded to this drug. While this drug would appear to have a very limited spectrum of in vivo antitumor activity, it possesses potent in vitro cytotoxic activity against a variety of tumor cell lines (4, 11, 12, 20). Our data suggest that auranofin does not alter cell cycle distribution or preferentially kill cells in logarithmic growth as do many cytotoxic antineoplastic agents. While the drug did inhibit DNA, RNA, and protein syntheses, the inhibition was not selective and occurred at concentrations which were acutely lethal to cells as measured by trypan blue exclusion. The equivalent IC50 values, as measured in the clonogenic and dye exclusion assays (Chart 4), along with the data outlined above, suggest a rapid cellular response to the cytotoxicity of auranofin unlike the more delayed response observed for cytotoxic antitumor agents, such as Adriamycin and actinomycin D (1). This rapid response was evident microscopically as cells treated at auranofin concentrations as low as 1 µM for 2 hr showed extensive morphological alterations including surface membrane pitting, cell rounding, detachment from the surface of the culture dish, and membrane lysis. Together, these data suggest that the rapid cellular response to the cytotoxic action of auranofin is due to its effects on cellular processes other than DNA, RNA, or protein synthesis.
with a variety of structural analogues of auranofin have identified the phosphine-gold moiety of the molecule as being required for in vitro cytotoxic and in vivo antitumor activities.

Serum proteins, especially serum albumin, play an important but poorly understood role in the disposition of a number of drugs and certain metals (23), including gold(I) thiolates. The binding of gold to serum albumin during chrysotherapy (8) following the in vivo administration of gold complexes to animals (10) and during the in vitro incubation of gold complexes with serum (2, 9) or purified protein (6) has been clearly demonstrated. As shown by our studies, increasing the concentration of FCS resulted in a decrease in the cytotoxic potency of auranofin (Chart 3A) and a proportional increase in protein-associated gold (Chart 9). This suggests that the cytotoxic action of the drug results from the non-protein-bound form of gold from auranofin. However, the extent of cell-associated gold in the presence of FCS (Chart 8) indicates that the gold from gold-protein complexes can become associated with the cells. For example, when cells were incubated with 2 μM auranofin, the inclusion of 10% FCS in the incubation medium produced an approximate 10-fold decrease in cytotoxic potency and the level of nonprotein gold, but only a 2- to 3-fold decrease in cell-associated gold (relative to those values measured in the absence of FCS). Our data also show that auranofin gold associated with cells is stable and does not dissociate within 1 hr in drug-free medium (Chart 7). The ability of 2-mercaptoethanol and dithiothreitol (not shown) to dissociate the cell-associated gold suggests a thiol-reversible interaction of the gold at either the membrane or intracellular level.

In conclusion, the in vivo antitumor activity of auranofin as evaluated in a spectrum of mouse tumor models is extremely limited. However, this drug has potent cytotoxic activity in vitro against a variety of tumor cell types. The data presented in this paper demonstrate that the cytotoxic effect of the drug is rapid and that there appears to be a direct relationship between cellular association of auranofin-derived gold and the cytotoxic effect of the drug. In addition, this cytotoxic effect is not mediated through a cell cycle-specific or -dependent mechanism nor is there evidence for a preferential inhibition of DNA, RNA, or protein synthesis. Further evaluation and definition of the cellular interactions of auranofin may lead to the design of a cytotoxic gold complex with a greater degree and spectrum of antitumor activity as well as additional insights into the cellular pharmacology of clinically established gold complexes in rheumatoid arthritis.

ACKNOWLEDGMENTS

We thank Judy Seaman for her excellent typographical assistance in preparing the manuscript. We also thank Dr. John Dent, Dr. Nabil Hanna, and Dr. C. H. Huang for useful discussions during the work and critical review of the manuscript.

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Consequently, our studies have been directed towards investigating the interaction of auranofin and its cellular metabolites with structural and enzymatic components of the cell surface and in the cytoplasm.

Association of gold from auranofin with cells in culture was time and temperature dependent. These findings are consistent with the time- (Chart 3A) and temperature-dependent (Chart 5) cytotoxic effects of the drug and suggest a relationship between gold binding and the cytotoxic effects of auranofin. Recent studies in our laboratory (12) and those reported by others (19)


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