Nontoxic Doses of Suramin Enhance Activity of Paclitaxel against Lung Metastases

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ABSTRACT

We recently reported that acidic (aFGF) and basic (bFGF) fibroblast growth factors confer a broad spectrum chemoresistance in solid tumors, and that suramin, an inhibitor of multiple growth factors including aFGF and bFGF, enhanced the in vitro antitumor activity of several anticancer drugs including paclitaxel (Song, S., et al., Proc. Natl. Acad. Sci. USA, 97; 8658–8663, 2000). The present study investigated in vitro and in vivo interaction between paclitaxel and suramin, using human PC3-LN cells which, upon i.v. injection into immunodeficient mice, yielded lung metastases in 100% of animals. In in vitro studies, conditioned medium (CM) obtained from histocultures of rat lung metastases induced a 3-fold resistance. The addition of suramin had no effect in the absence of CM but reversed the CM-induced resistance; calculations based on the IC50 values indicate a complete reversal in the presence of <20 μM suramin. Analysis by the combination index method indicates a synergistic interaction between paclitaxel and suramin. In in vivo studies, animals with well-established lung metastases (at least five nodules of 1 mm in diameter) were treated i.v. with paclitaxel (15 mg/kg) and suramin (10 mg/kg) administered twice weekly for 3 weeks. Single-drug therapy with paclitaxel or suramin did not reduce body weight. Suramin alone had no antitumor activity. Paclitaxel alone reduced the tumor size by ~75%, reduced the density of nonapoptotic cells by ~70% in residual tumors, and enhanced the fraction of apoptotic cells by ~3-fold. The addition of suramin to paclitaxel therapy enhanced the antitumor effect, resulting in an additional 5-fold reduction of tumor size, an additional 9-fold reduction of the density of nonapoptotic cells, and an additional 30% increase in the apoptotic cell fraction. These data indicate significant enhancement of the efficacy of paclitaxel by suramin and support the use of nontoxic doses of suramin with paclitaxel in the treatment of lung cancer.

INTRODUCTION

Tumor metastasis is the major cause of treatment failure for cancer patients (1). About 60% of patients have microscopic or clinically evident metastases at the time of diagnosis of primary tumors. Surgery and localized radiation are of limited value in treating widely spread metastases. Systemic chemotherapy constitutes an important treatment modality for metastatic diseases. The differential response of primary and metastatic tumors to chemotherapy has been documented in preclinical experimental models and in clinical practice (reviewed in Ref. 2). In general, metastatic tumors are less sensitive to chemotherapy compared with their corresponding primary tumors (2–4).

The microenvironment of the tumor-bearing organ may play an important role in lowering the chemosensitivity of metastatic tumors (reviewed in Refs. 2, 3). For example, murine colon tumor cells implanted s.c. or into different visceral organs show differential sensitivity to doxorubicin; with the s.c. tumor being sensitive, whereas the tumors at the metastatic sites (i.e., lung and liver) are insensitive (4). For this tumor, the chemoresistance of metastatic tumors was correlated with Pgp overexpression; the Pgp expression was transient, and culturing these cells as monolayers resulted in the reversal of Pgp expression and chemoresistance. On the other hand, clinical studies show that inhibition of drug efflux proteins including Pgp does not significantly improve the effectiveness of chemotherapy in patients (5, 6), suggesting the existence of other chemoresistance mechanisms.

Using the transplantable, metastatic rat prostate MAT-LyLu tumor, we have shown that the antitumor activity of paclitaxel in lymph node metastases was 20-fold lower than in s.c. implanted primary tumors. When the metastatic tumor was reimplanted at the s.c. site, the resistance was lost in the second generation primary tumor but regained in the second generation metastases. Furthermore, we found that the chemoresistance in metastatic tumors is not attributable to reduced intracellular drug accumulation or retention (7). We subsequently showed that the chemoresistance in lung metastases is caused by aFGF and bFGF. These two proteins at clinically relevant concentrations induce an up-to-10-fold resistance to drugs with diverse structures and action mechanisms. The resistance was not attributable to an alteration in drug accumulation. Inhibitors of aFGF and bFGF, including the monoclonal antibodies and suramin, completely reverse the FGF-induced resistance (7, 8).

In our earlier study, the suramin concentration required to completely reverse the FGF-induced resistance to paclitaxel, doxorubicin, and 5-fluorouracil was 15 μM. This suramin concentration does not cause cytotoxicity in cultured human tumor cells. Furthermore, we found that suramin, at a dose that delivers peak plasma concentration of 50 μM, significantly enhances the therapeutic efficacy of doxorubicin against lung tumors in immunodeficient mice, resulting in shrinkage and eradication of well-established tumors in animals. The enhanced therapeutic efficacy attributable to suramin was achieved without enhancing the host toxicity (8).

Our earlier in vivo study used doxorubicin to determine the effect of the microenvironment of metastatic organs on chemosensitivity. The goal of the present study was to evaluate whether suramin can be used to enhance the therapeutic efficacy of chemotherapy in lung cancer, with the overall goal of identifying a more effective treatment for this disease. Because paclitaxel is among the most effective agents against lung tumors (9, 10), the present study was performed using suramin and paclitaxel. Because we have shown that the FGF proteins expressed in lung metastases are the cause of the drug resistance, we considered it more important to use a model that resides in the lungs than to use s.c. implanted tumors derived from lung tumor cells. Accordingly, in vivo studies were performed using human prostate PC3-LN tumor cells which, when injected i.v. in immunodeficient mice, result in well-established lung xenograft tumors within 4–6 weeks with a 100% success rate (11). In vitro studies were performed to identify the paclitaxel and suramin concentrations that produced the highest synergy and thereby identify the doses of the two drugs for the in vivo studies.

MATERIALS AND METHODS

Chemicals and Reagents. Paclitaxel was obtained from Bristol-Myers Squibb (Princeton, NJ), the National Cancer Institute (Bethesda, MD), or Hande Tech (Houston, TX); suramin from Sigma Chemical Co. (St. Louis, MO); ceftotaxime sodium from Hoechst-Roussel (Somerville, NJ); cell culture
supplies from Life Technologies, Inc. (Grand Island, NJ); and BrdUrd ELISA kit from Boehringer Mannheim (Indianapolis, IN).

**Cell and Tumor Cultures.** To induce paclitaxel resistance in the *in vitro* studies, we used the CM of lung metastases derived from s.c. implanted rat MAT-LyLu tumors. The lung metastases were cultured as histocultures, and CM was collected in a ratio of 50 ml CM:100 mg tumors, as described previously. CM collected by this method contains about 0.3 ng/ml aFGF and 0.9 ng/ml bFGF (8). Human prostate PC3-LN tumor cells were a gift from Dr. Joy Ware (Virginia Commonwealth University, Richmond, VA). Tumor cells were maintained as monolayer cultures at 37°C in a humidified atmosphere containing 5% CO2 in RPMI 1640 supplemented with 9% fetal bovine serum, 2 mM l-glutamine, 90 μg/ml gentamicin, and 90 μg/ml cefotaxime.

**Drug Solutions.** Suramin was dissolved in physiological saline. The stock solutions of paclitaxel for the *in vitro* studies were prepared by dissolving paclitaxel in 100% ethanol at a concentration of 1 mM. The final concentration of ethanol in the drug treatment was <0.1%, which had no effect on cell proliferation. For the *in vivo* studies, paclitaxel was dissolved in Cremophor EL:ethanol (50:50), at a concentration of 15 mg/ml, and diluted with 9 volumes of physiological saline before administration to animals. Drug solutions were stored at −20°C or −70°C.

**In Vitro Drug Activity Evaluation.** Cells were treated with drugs for 4 days. In the samples where CM was used to induce resistance, cells were pretreated with CM for 4 days before drug treatment and also during drug treatment. The medium was renewed every other day.

Drug-induced cytotoxicity was measured as the inhibition of BrdUrd incorporation using ELISA. The relationship between drug concentration and effect was analyzed for IC50 values (drug concentrations that produce 50% inhibition) by computer fitting the concentration-response curves using nonlinear least squares regression (NLLIN; SAS, Cary, NC), as previously described (12).

**Synergy between Paclitaxel and Suramin in Cultured Cells.** The nature of the interaction between paclitaxel and suramin was evaluated using the fixed-ratio method. In the evaluation of concentration-response curves, the ratios between paclitaxel concentrations and suramin concentrations were kept constant. Cells were treated with solutions containing the two drugs at 0.001% to 100% of their respective initial concentrations. The initial paclitaxel concentrations were kept constant at 2.5 μM, whereas the initial suramin concentrations were varied by 80-fold from 90 to 7200 μM.

**Analysis of in Vitro Synergy Data.** The nature of the interaction between paclitaxel and suramin, in the presence of CM, was analyzed by the combination index method (13). The combination index was calculated using Equation A.

\[
\text{Combination Index} = \frac{IC_{\text{Pac,Comb}} + IC_{\text{Sur,Comb}}}{IC_{\text{Pac}}} \quad \frac{IC_{\text{Sur}}}{IC_{\text{Pac}}} \quad \frac{IC_{\text{Sur}}}{IC_{\text{Pac}}} \quad \frac{IC_{\text{Sur}}}{IC_{\text{Pac}}}
\]

where ICp and ICs are the concentrations of paclitaxel and suramin needed to produce a given level of cytotoxicity when used alone, whereas ICp,Comb and ICs,Comb are the concentrations needed to produce the same effect when used in combination. A combination index value of 1 indicates additive interaction, values <1 indicate synergistic action, and values >1 indicate antagonistic interaction. As shown in “Results,” the synergy between paclitaxel and suramin was attributable to the reversal of the CM- or GEM-induced resistance to paclitaxel by suramin. The extent of reversal of drug resistance was calculated using Equation B.

\[
\text{Extent of Reversal} = \frac{IC_{\text{Pac,CM}} - IC_{\text{Pac,CM,Sur}}}{IC_{\text{Pac,CM,Sur}}} \quad \frac{IC_{\text{Pac,CM,Sur}}}{IC_{\text{Pac,CM,Sur}}}
\]

where ICp,CM is the IC50 of paclitaxel in the presence of CM, ICp,CM,Sur is the IC50 of paclitaxel in the presence of CM plus suramin, and ICp is the IC50 of paclitaxel without CM or suramin.

**Animal and Drug Treatment Protocols.** Male BALB/c nu/nu mice (6–8 weeks of age) were used. Animal care was in accordance with institutional guidelines. Human PC3-LN cells (106 in 0.1 ml physiological saline) were injected i.v. via a tail vein. After 5 weeks, tumor establishment was determined by visual examination of the lungs of two randomly selected animals, and drug treatment in the remaining animals was initiated when these two animals showed at least five tumor nodules of ~1 mm in diameter. Mice received i.v. injection, over 1 min, via a tail vein, of 200 μl of a Cremophor EL/ethanol/saline solution delivering 15 mg/kg paclitaxel, 10 mg/kg suramin, or a combination of both drugs, twice weekly for 3 weeks. The control group received only the vehicle. Pharmacokinetic studies in normal mice (i.e., without tumors) indicated that the selected doses yielded a peak plasma concentration of 50 μM and a concentration of 1 μM at 72 h for suramin and a peak plasma concentration of 1 μM and a concentration of 4 nM at 72 h for paclitaxel.4 These paclitaxel concentrations were in the range of its IC50 in monolayer cultures of PC3-LN cells, and the suramin concentrations were sufficient to reverse the GEM-induced chemoresistance (see “Results”).

**Histological Evaluation of Tumors.** Three days after completion of drug treatments, animals were euthanized and their lungs were removed, fixed in Bouin’s solution to visualize tumor nodules, and then processed for histological evaluation. Histological sections (5 μm) at a depth of between 200–300 μm from the ventral surface and containing all five lobes of the lungs were obtained. The lung surface area (counted as the number of pixels) occupied by the tumor was calculated as a fraction of the total lung area, using Adobe PhotoShop. We also determined microscopically the number of tumor cells in residual tumors and the fraction of apoptotic cells in each tumor. Cells that show condensed nuclei and blebbing were considered apoptotic; we and others have shown that apoptotic cells identified by these morphological changes are identical to the apoptotic cells identified by the TUNEL method (14, 15). Because apoptotic cells disappear over time, a second measure of the extent of apoptosis was the density of nonapoptotic cells in the residual tumors. This was determined by counting the number of nonapoptotic tumor cells in randomly selected microscopic fields at x400. On average, we counted 1230 ± 760 cells/animal in the control and suramin groups and 530 ± 530 cells in the paclitaxel group. In the case of combination therapy, where few tumor cells remained after treatment, we counted all residual cells (150 ± 160 cells, between 16–525 cells/animal).

**RESULTS**

**Reversal of CM-induced Paclitaxel Resistance by Suramin.** Fig. 1 shows that pretreatment of PC3-LN cells with CM resulted in a 3-fold resistance to paclitaxel. As single agent, the IC50 of suramin was 98 ± 2.2 μM and 308 ± 8.8 μM (mean ± SD) in the absence and presence of CM, respectively (Fig. 2). In the absence of CM, suramin had no effect on the paclitaxel activity. However, in the presence of CM, the addition of suramin reversed the CM-induced resistance.

Table 1 summarizes the IC50 values for paclitaxel and suramin in combination therapy and the extent of reversal of the CM-induced resistance by suramin. It is noted that the initial suramin concentrations shown in Table 1 represent the concentrations of the solution used to prepare the up to 100,000-fold serially diluted solutions. The actual effective suramin concentrations, i.e., IC50, are much lower and typically <0.5% of the initial concentrations. Whereas the extent of reversal increased with the suramin concentration, relatively low suramin concentrations were required to reverse the CM-induced resistance. For example, ~90% of the CM-induced resistance was reversed for combinations using a paclitaxel:suramin concentration ratio of 1:288 (i.e., combinations with initial concentrations of 2.5 μM paclitaxel plus 720 μM suramin); the corresponding IC50 values were ~10 nm for paclitaxel and ~3 μM for suramin. Complete reversal required a 10-fold higher suramin concentration (i.e., initial concentrations of 7,200 μM); the corresponding IC50 values were ~8 nm paclitaxel and ~23 μM for suramin. As shown in Fig. 2, suramin had no cytotoxicity at ≤20 μM.

Fig. 3 shows the results of the combination index analysis for the two combinations containing paclitaxel:suramin concentration ratios of 1:36 (i.e., initial concentrations of 2.5 μM paclitaxel plus 90 μM suramin) and 1:72, the combination indices were indistinguishable from 1.0 at effect levels of ≤50% but were significantly less than 1.0 at higher effect levels. For the remaining four combinations contain-

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4 Unpublished data.
Fig. 1. Reversal of CM-induced resistance to paclitaxel by suramin in vitro. CM of histocultures of rat MAT-LyLu lung metastases was used to induce resistance in human PC3-LN tumor cells. Drug effect was measured as the inhibition of BrdUrd incorporation. The concentrations of paclitaxel and suramin were kept at fixed ratios as described in “Materials and Methods.” The X axis describes the drug concentrations relative to the initial concentrations, with the initial concentrations equal to 100%. Right, with CM: ●, control (i.e., no CM, no suramin, left solid curve). CM-treated control (○, right solid curve). Dotted curves from right to left, different combinations of paclitaxel and suramin containing increasing suramin concentrations: ●, 2.5 μM paclitaxel plus 90 μM suramin; ○, 2.5 μM paclitaxel plus 180 μM suramin; □, 2.5 μM paclitaxel plus 720 μM suramin; ■, 2.5 μM paclitaxel plus 3600 μM suramin; □, 2.5 μM paclitaxel plus 7200 μM suramin. Left, No CM. Same conditions and symbols as in the panel on the right. All curves overlapped with each other. Results of a representative experiment. Mean of five replicates. For clarity, SDs (0.26–4.25%) are not included.

Fig. 2. Cytotoxicity of suramin. Human PC3-LN tumor cells were treated with suramin, in the absence (○) and presence (●) of CM. Results of a representative experiment. Mean and one SD (n = 5). Some SDs are smaller than the symbols.

Synergy between Paclitaxel and Suramin in Vivo. Results of the in vivo antitumor activity evaluation are summarized in Fig. 4 and Table 1. Suramin alone had no antitumor effect or toxicity, consistent with the results in other mouse tumor models (8, 16, 17). Single-drug therapy with paclitaxel or suramin did not reduce body weight. Paclitaxel alone significantly reduced tumor size by ~75%, reduced the density of nonapoptotic cells by ~70%, and increased the fraction of apoptotic cells in the residual tumors by ~3-fold. Addition of suramin to paclitaxel therapy significantly enhanced the antitumor effect, resulting in an additional 5-fold reduction of tumor size, an additional 9-fold reduction in the density of nonapoptotic cells, and an additional 30% increase in the apoptotic cell fraction. It is of interest that a small fraction of animals (≤30%) in the control and single drug therapy groups showed extrapulmonary tumors in the neck and diaphragm, whereas no extrapulmonary tumors were found in the combination therapy group.

DISCUSSION

Several growth factors, including bFGF, IGF, and epidermal growth factor, have been shown to induce tumor resistance to anticancer drugs (18–25). Our earlier study also shows that aFGF, although not required to induce drug resistance, enhanced the FGF effect such that the two proteins, at clinically relevant concentrations, can induce a 10-fold resistance. The clinical relevance of the FGF-resistance mechanism is supported further by our observation in a separate study where FGF expression was found to be a better predictor of paclitaxel resistance in human tumors, as compared with other known prognostic indicators such as mutated p53, overexpres-

Table 1 Reversal of CM-induced paclitaxel resistance by suramin

<table>
<thead>
<tr>
<th>Condition (initial paclitaxel-suramin concentrations, in μM)</th>
<th>Paclitaxel concentration at 50% effect (μM)</th>
<th>Suramin concentration at 50% effect (μM)</th>
<th>Resistance reversal (%)</th>
<th>Combination index</th>
<th>Synergy (fold)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No CM, no suramin</td>
<td>7.7 ± 0.1</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>No CM, + suramin</td>
<td>8.0 ± 1.0</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>+ CM, no suramin</td>
<td>23.0 ± 0.7</td>
<td>1.1 ± 0.1</td>
<td>9 ± 9</td>
<td>0.94 ± 0.1</td>
<td>1.06 ± 0.7</td>
</tr>
<tr>
<td>+ CM (2.5/50)</td>
<td>21.6 ± 0.8</td>
<td>14 ± 1</td>
<td>21 ± 15</td>
<td>0.86 ± 0.1</td>
<td>1.17 ± 0.16</td>
</tr>
<tr>
<td>+ CM (2.5/180)</td>
<td>19.7 ± 1.9</td>
<td>1.4 ± 0.1</td>
<td>69 ± 4</td>
<td>0.55 ± 0.02</td>
<td>1.83 ± 0.07</td>
</tr>
<tr>
<td>+ CM (2.5/360)</td>
<td>12.5 ± 0.8</td>
<td>1.8 ± 0.1</td>
<td>87 ± 4</td>
<td>0.43 ± 0.02</td>
<td>2.32 ± 0.13</td>
</tr>
<tr>
<td>+ CM (2.5/720)</td>
<td>9.7 ± 0.7</td>
<td>2.8 ± 0.2</td>
<td>94 ± 5</td>
<td>0.41 ± 0.03</td>
<td>2.45 ± 0.17</td>
</tr>
<tr>
<td>+ CM (2.5/3600)</td>
<td>8.5 ± 0.6e</td>
<td>12.3 ± 0.9</td>
<td>98 ± 3</td>
<td>0.45 ± 0.02</td>
<td>2.39 ± 0.09</td>
</tr>
<tr>
<td>+ CM (2.5/7200)</td>
<td>7.9 ± 0.4f</td>
<td>22.8 ± 1.1</td>
<td>98 ± 3</td>
<td>0.45 ± 0.02</td>
<td>2.39 ± 0.09</td>
</tr>
</tbody>
</table>

* The IC₅₀ of suramin alone was 98 ± 2.2 μM in the absence of CM and 308 ± 8.8 μM in the presence of CM (see Fig. 2).

b NA, not applicable.

c P > 0.05 compared with the control group (no CM and no suramin).

d P < 0.05 compared with the control group (no CM and no suramin).

e P < 0.05 compared with the CM-treated and no suramin group.
sion of Bcl2 and Pgp, and tumor pathology (grade, stage, and labeling index; Ref. 26).

Results of the present study indicate that suramin, a nonspecific inhibitor of aFGF and bFGF, reversed the CM-induced resistance to paclitaxel in tumor cells as well as enhanced the activity of paclitaxel in animals bearing lung metastases. The synergy between suramin and paclitaxel was achieved at low and nontoxic concentrations and doses of suramin.

In addition to aFGF and bFGF, suramin also inhibits the action of several other polypeptide growth factors, including platelet-derived growth factor, vascular endothelial growth factor, transforming growth factor-β, and IGF-1 (27–31). We elected to use suramin to reverse the FGF-induced resistance in part because clinical pharmacological data are readily available for this compound. Suramin has moderate activity in prostate cancer (32–35); the therapeutic plasma concentration is between 100 and 200 μM (140–280 μg/ml; Ref. 36).

The two important limitations of suramin are: (a) its broad spectrum of toxicity including neurotoxicity, renal toxicity, adrenal insufficiency, and immune- and glycosaminoglycans anticoagulant-mediated blood dyscrasias (37–43); and (b) difficulty in dose administration because of its exceedingly long terminal plasma half-life of >21 days (44, 45). The relatively modest activity of suramin led to the development of combination therapies of suramin with other agents, where suramin was again given at doses that resulted in a >200 μM

Fig. 3. Synergy between paclitaxel and suramin. Results depicted in Fig. 1 were analyzed by the combination index method. Combination indices were plotted as a function of the effect level, i.e., a percentage of inhibition of BrdUrd incorporation. A combination index of <1 indicates synergy. Top to bottom, combinations of paclitaxel and suramin containing increasing suramin concentrations: 2.5 μM paclitaxel plus 90 μM suramin (○); 2.5 μM paclitaxel plus 180 μM suramin (○); 2.5 μM paclitaxel plus 360 μM suramin (○); 2.5 μM paclitaxel plus 720 μM suramin (○); 2.5 μM paclitaxel plus 3600 μM suramin (○); 2.5 μM paclitaxel plus 7200 μM suramin (○). Results of a representative experiment. Mean and one SD (n = 5). Some SDs are smaller than the symbols.

Fig. 4. Enhancement of in vivo antitumor activity of paclitaxel by suramin. Animals with well-established PC3-LN lung metastases were treated with physiological saline (i.e., control), suramin (10 mg/kg), paclitaxel (15 mg/kg), or a combination of both drugs. Top, visible, large tumors on the ventral and dorsal surfaces of the lungs in all animals in the control and suramin groups, small tumors in the paclitaxel group, and yet-smaller tumors in the combination group. Bottom, histological sections (×100), with tumors outlined in red.
concentration; these combinations have either shown limited benefit or have resulted in toxicity that discouraged additional evaluation of these regimens (46–51).

The major difference between the previous preclinical and clinical studies with suramin and our study is the intended use of suramin and, accordingly, the selection of the dose/concentration. In previous studies, suramin was used as a therapeutic agent and, therefore, required the maintenance of a target concentration of $\geq 200 \mu M$. In the current study, suramin is used to reverse the FGF-induced resistance, an effect requiring $\leq 20 \mu M$, which has no cytotoxicity in cultured tumor cells nor toxicity in animals or patients. Another important consideration is the concentration-dependent effect of suramin on cell cycle kinetics. Suramin at concentrations above 50–100 $\mu M$ arrests cells in the G1 phase (51–53). A blockage in the G1 phase may protect cells from the action of other agents that exert their effect during the later phases, such as the S and M phases. An example is the combination of suramin and radiation; suramin at 50 $\mu M$ concentration caused cell cycle arrest in the G2 phase, which in turn resulted in antagonism with radiation that is most effective in the G2-M phase (53). In contrast, the $\leq 20 \mu M$ concentration that we used to reverse the FGF-induced resistance does not cause G1 arrest and therefore is not expected to negatively affect the activity of other treatments.

In summary, results of the present study indicate that low and nontoxic doses of suramin significantly enhance the in vitro and in vivo antitumor activity of paclitaxel, and support a new treatment paradigm using combinations of chemotherapy with aFGF/bFGF inhibitors. On the basis of these findings, a Phase II/III trial of suramin, paclitaxel and carboplatin in non-small lung cancer patients has been initiated in our institution.

REFERENCES


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