Differentiation Therapy of a Myelomonocytic Leukemia (c-WRT-7) in Rats by Injection of Lipopolysaccharide and Daunomycin

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ABSTRACT

We examined the therapeutic effect of lipopolysaccharide (LPS), a differentiation inducer, in combination with daunomycin, an antileukemia drug possessing differentiation-inducing potential, on a rat myelomonocytic leukemia (c-WRT-7). c-WRT-7 cells were found to differentiate into macrophage-like cells and to lose their growth capacity both in vitro and in vivo after incubation with LPS. Morphological differentiation of c-WRT-7 cells was observed in diffusion chambers which had been inserted into the abdominal cavity of syngeneic WKA rats given injections of LPS. A series of i.p. injections of LPS resulted in the complete inhibition of the leukemia development in about 60% of the rats while the remaining rats showed a significant prolongation of survival time when they were given i.p. injections of LPS-sensitive c-WRT-7 cells. The effect of LPS was minimal, however, in those rats which had been given i.p. injections of LPS-hyporesponsive c-WRT-7 cells. Although an i.v. injection of 100 untreated c-WRT-7 cells was enough to kill the syngeneic rats, combination treatment with LPS and daunomycin was able to inhibit completely the development of leukemia in those rats which had been given i.v. injections of LPS-sensitive c-WRT-7 cells, whereas the same treatments were only partially effective in the prolongation of survival among those rats which had been given i.v. injections of LPS-hyporesponsive c-WRT-7 cells.

Our studies show that LPS was capable of curving a proportion of rats and that it significantly prolonged the survival of the remainder who had received a transplantation of the differentiation-sensitive leukemia cells; this action was significantly enhanced by the associated administration of daunomycin.

INTRODUCTION

Recently, several reports have suggested that myeloid leukemias in humans are able to differentiate in response to various treatments such as low dose 1-β-D-arabinofuranosylcytosine (1), Harringtonine (2), aclacinomycin A (3), butyrate (4), retinoic acid (5), and high dose 1-β-D-arabinofuranosylcytosine in combination with asparaginase (6). At the same time, a proposal to control leukemias by the induction of differentiation has aroused great interest because its mechanism is different from the chemotherapy currently in use which is based on the theory of "total cell kill" (7) and because it is expected to be less toxic than such cytotoxic chemotherapies. Several leukemia cell lines have been used to detect differentiation inducers and to analyze differentiation mechanisms in vitro (8). Except for M1 leukemia cells, however, a detailed examination of the in vivo differentiation of leukemia cells has not yet been carried out (8).

The purpose of this study was to explore whether LPS, a differentiation inducer, alone or in combination with daunomycin, a chemotherapeutic drug having differentiation-inducing potential, is able to induce the in vivo differentiation of the c-WRT-7 leukemia cells and whether it is able to cause the subsequent inhibition of leukemia development in syngeneic rats.

MATERIALS AND METHODS

Rats. Twelve- to 16-week-old inbred WKA rats were obtained from the Experimental Animal Institute, Hokkaido University School of Medicine, Sapporo, Japan.

Cultured Cells. The cells used came from a parent line (P2), a subline (P2NS), and a clone (P2S) which derived from a c-WRT-7 cell line which isolated from a myelomonocytic leukemia induced by a neonatal injection of Rauscher leukemia virus in a WKA rat (9, 10). These leukemia cell lines were maintained in a suspension culture in RPMI 1640 supplemented with 10% fetal calf serum (heat inactivated at 56°C for 30 min), streptomycin (50 µg/ml), and penicillin G (50 units/ml) in a humidified 5% CO₂ atmosphere at 37°C.

Administration of LPS and Daunomycin. Preparations of LPS (Boivin type) from Escherichia coli 055:B5 were purchased from the Sigma Chemical Co., St. Louis, MO. The LPS was dissolved in sterilized phosphate-buffered saline (0.2 g KCl, 0.2 g KH₂PO₄, 8 g NaCl, and 2.16 g NaHPO₄·7H₂O per liter), and 1 ml of the LPS solution was injected into rats 4 times i.p. or 5 times i.v. Daunomycin was supplied by Meiji Seika, Ltd., Tokyo, Japan. One ml of daunomycin solution was injected i.v. at 1 mg/kg into rats 3 times. When LPS and daunomycin were administered at the same time, these drugs were mixed in a 1-ml syringe immediately before the injection and 1 ml of the mixed solution was injected i.v. into rats. The first injection of LPS and/or daunomycin was made 3 h after the tumor challenge.

Assay for Phagocytosis. The phagocytic capacity of the leukemia cells was quantified by determining both the percentage and the absolute numbers of those cells which ingested latex beads (Bacto Latex 0.81; Difco, Detroit, MI). The cells were seeded at a concentration of 2 × 10⁶ cells/ml into 2 ml of culture medium and incubated with 0.1 ml of an appropriate concentration of the drug solution. After 48 h incubation, the cells were further incubated with 0.25% (v/v) solution of latex particles for 3 h. The cells were then washed 3 times and resuspended in about 0.2 ml of the medium; those cells which ingested more than 5 latex particles were defined as phagocytosis positive. More than 300 viable cells were examined microscopically.

Diffusion Chambers. The diffusion chamber technique was performed according to the description given by Benestad (11). Briefly, the chambers were constructed by gluing Millipore filters (type HA; pore size, 0.45 µm) with Millipore MF cement to each side of a Millipore Plexiglas ring (10-mm inner diameter, 2 mm thick). The chambers were sterilized with ethylene oxide and tested for leaks before being filled with 0.1 ml of cell suspension (5 × 10⁶ cells) and sealed. Two chambers were inserted into the peritoneal cavity of each rat and the rats were given i.p. injections of 1 ml of the LPS solution (20 µg/kg) at 2, 3, and 4 days after implantation. The chambers were harvested at 5 days and were shaken for 1 h at room temperature in 0.5% Pronase and 5% Ficoll in Hank's balanced salt solution. For a morphological assessment of the cells, cytoplasm smear preparations of cell suspensions were prepared with a Shandon Cytospin centrifuge (Shandon Southern Products, Ltd., United Kingdom) and stained with May-Grünwald-Giemsa.

Electron Microscopic Examination. For transmission electron microscopy, c-WRT-7 cells in suspension were fixed in 2% glutaraldehyde in 0.1 M cacodylate buffer (pH 7.4) for 2 h, postfixed with 2% osmium tetroxide in buffer for 2 h, and stained with 1% uranyl acetate in an appropriate concentration of the drug solution. After 48 h incubation, the cells were further incubated with 0.25% (v/v) solution of latex particles for 3 h. The cells were then washed 3 times and resuspended in about 0.2 ml of the medium; those cells which ingested more than 5 latex particles were defined as phagocytosis positive. More than 300 viable cells were examined microscopically.

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2The abbreviation used is: LPS, lipopolysaccharide.
DIFFERENTIATION THERAPY OF A RAT LEUKEMIA

RESULTS

Differentiation Induction and Growth Inhibition of c-WRT-7 Cells by LPS. In vitro growth of LPS-sensitive cell lines (P2 and P2S) was inhibited by treatment with LPS in a dose-dependent manner, whereas the growth inhibition by LPS was minimal in the LPS-hyporesponsive P2NS cell line (Fig. 1A). After treatment of the sensitive P2 and P2S cells with LPS for 2 days, the increase in the numbers of phagocytic cells and the concurrent decrease in the numbers of nonphagocytic cells with the increasing concentrations of LPS were so sharp that the number of phagocytic cells surpassed the number of nonphagocytic cells at 0.1 μg/ml of LPS (Fig. 1B). In the hyporesponsive P2NS cells, however, the gradually increasing numbers of phagocytic cells came to surpass the gradually decreasing numbers of nonphagocytic cells only at 10.0 μg/ml of LPS. The viability of the LPS-treated cells examined by dye exclusion was more than 80% throughout the observation period. Figs. 2 and 3 show morphological changes discovered by electron microscopy in the differentiating c-WRT-7 cells after treatment with 1 μg/ml of LPS for 2 days.

Loss of Transplantability of LPS-treated c-WRT-7 Cells in Syngeneic Rats. Table 1 shows the effect of in vitro treatment with LPS on the transplantability of P2 cells in syngeneic rats. Twenty days after the i.v. injection of 100 untreated P2 cells, all the recipient animals died of the leukemia. After P2 cells were treated with 10 μg/ml of LPS for 2 days followed by a 5-day incubation in a LPS-free medium, 95% of the cells assumed a macrophage morphology and attached themselves to the plastic dish. These cells, however, were easy to detach by exposing them to 0.02% EDTA for 5 min. This in vitro LPS treatment caused the loss of leukemogenicity in syngeneic rats.

Fig. 1. A, growth of c-WRT-7 cells (P2NS, P2, and P2S) in the presence of LPS. Cultures were initiated at 10⁵ cells/ml with (Ο) 0 μg/ml, (△) 0.1 μg/ml, or (●) 1.0 μg/ml LPS. Viable cell counts were made on days 1, 2, and 3. B, in vitro induction by LPS of phagocytosis in P2NS, P2, and P2S cells. The numbers of phagocytic cells and nonphagocytic cells were determined 2 days after seeding the cells with LPS. ○, number of phagocytic cells; ●, number of nonphagocytic cells.

Fig. 2. Scanning electron micrographs of c-WRT-7 cells. Bar, 5 μm. A, untreated P2 cells. The cells show microvilli. B, P2 cells treated by LPS (1 μg/ml) for 2 days. The cells show extensive membrane ruffles.

even when \(5 \times 10^4\) LPS-treated cells had been given i.v. injections.

**Differentiation of c-WRT-7 Cells in Diffusion Chambers.** In order to confirm the differentiation of the leukemia cells in vivo by LPS treatment, the diffusion chamber technique was used. P2 cells were seeded at the number of \(5 \times 10^4\) cells/chamber. Six chambers were used for each group to determine the mean numbers of the cells recovered and to assess the morphological differentiation. Fig. 4 shows that LPS promoted the differentiation of P2 cells in the diffusion chamber; in LPS-injected rats, \(120 \times 10^4\) cells were recovered; 37% were macrophage-like, 42% were in an intermediate stage of differentiation, while

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### Table 1 Transplantability of c-WRT-7 cells in syngeneic rats after incubation with LPS

<table>
<thead>
<tr>
<th>Incubation with LPS</th>
<th>No. of cells transplanted*</th>
<th>No. died/ no. used</th>
<th>Mean survival days ± SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>+</td>
<td>(10^3)</td>
<td>0/14</td>
<td>-</td>
</tr>
<tr>
<td>+</td>
<td>(10^4)</td>
<td>0/6</td>
<td>-</td>
</tr>
<tr>
<td>+</td>
<td>(5 \times 10^4)</td>
<td>0/6</td>
<td>-</td>
</tr>
<tr>
<td>-</td>
<td>(10^3)</td>
<td>5/5</td>
<td>20.7 ± 1.4</td>
</tr>
<tr>
<td>-</td>
<td>(10^4)</td>
<td>6/6</td>
<td>19.3 ± 1.1</td>
</tr>
<tr>
<td>-</td>
<td>(10^5)</td>
<td>6/6</td>
<td>16.8 ± 0.8</td>
</tr>
<tr>
<td>-</td>
<td>(10^6)</td>
<td>3/3</td>
<td>15.0 ± 1.0</td>
</tr>
</tbody>
</table>

* WKA rats were inoculated i.v. with P2 cells.

* The cells were treated by incubation in LPS (1 \(\mu g/ml\)) for 2 days followed by a 5-day incubation in a LPS-free medium.

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Fig. 3. Transmission electron micrographs of c-WRT-7 cells. **A**, untreated P2 cells. \(\times 6000\). **B**, P2 cells treated by LPS (1 \(\mu g/ml\)) for 2 days. \(\times 4800\). The cells show an increase in the numbers of vesicles and Golgi apparatus as well as an indentation of the nucleus.
Inhibition of the Leukemia Development by Injections of LPS in Rats. The loss of leukemogenicity of the in vitro LPS-treated c-WRT-7 cells in syngeneic rats and confirmation of the differentiation of the leukemia cells in the diffusion chambers led us to make an in vivo examination of the therapeutic effects of LPS in rats bearing the leukemia cells. Groups of rats were given i.p. injections of $10^3$ P2NS, P2, or P2S cells and received the first injection of LPS 3 h after the leukemia cell challenge. LPS at a maximal dose of 62.5 μg/kg, which corresponds to the one-twentieth of the median lethal dose, or at smaller doses (20 and 2 μg/kg) was given i.p., every other day, 4 times in total. Fig. 5 shows that treatment with 62.5 μg/kg of LPS not only significantly increased survival days but also inhibited completely the leukemia development in 60% of the rats when rats had been given i.p. injections of the sensitive P2 or P2S cells, whereas the effect of LPS on the prolongation of the survival days was minimal but nevertheless significant in the rats bearing the hyporesponsive P2NS cells. LPS (20 μg/kg) was equally as effective in the inhibition of the leukemia development as LPS (62.5 μg/kg) in the P2S cells.

Effect of a Combined Treatment with LPS and Daunomycin on the Inhibition of Leukemia Development in Rats. Another aim of this study was to examine whether the therapeutic effect of LPS could be enhanced by a combined treatment with an antileukemia drug having a differentiation-inducing potential. Table 2 shows the effect of five chemotherapeutic drugs with distinct cytotoxic action on the induction of differentiation among P2 cells. Differentiation was assessed by the phagocytic capacity quantified by the determination of both percentage and absolute numbers of the phagocytic cells. A relatively low but significant number of functionally differentiated P2 cells was observed after treatment with two antileukemia drugs, daunomycin and aclacinomycin A.

Although Fig. 5 shows that LPS was capable of curing a proportion of rats which had received an i.p. transplantation of the leukemia cells, preliminary studies revealed that LPS was unable to bring about any cure in rats which had received an i.v. transplantation of the leukemia cells. Accordingly, we examined the combined effects of LPS and daunomycin in rats which had received an i.v. transplantation of the leukemia cells. Table 3 shows that a series of i.v. injections of 62.5 μg/kg of...
LPS resulted in significant prolongation of survival days in those rats which had been given i.v. injections of 10^8 LPS-sensitive P2S cells (25.3 days, P < 0.05). Daunomycin inhibited completely the development of the leukemia in one of five rats while the remaining rats showed a significant prolongation of the survival days (27.5 days, P < 0.01). The combined treatment with LPS and daunomycin resulted in the complete inhibition of the leukemia development in all the treated rats.

On the other hand, Table 4 shows that the same treatment schedule of LPS as given in Table 3 was not effective in prolongation of survival days in the rats which had been given i.v. injections of 10^8 LPS-sensitive P2S cells (25.3 days, P < 0.05). Daunomycin inhibited completely the development of the leukemia in one of five rats while the remaining rats showed a significant prolongation of the survival days (27.5 days, P < 0.01). The combined treatment with LPS and daunomycin resulted in the complete inhibition of the leukemia development in all the treated rats.

**DISCUSSION**

The present study clearly demonstrates that rat myelomonocytic leukemia (c-WRT-7) cells are able to differentiate into macrophage-like cells in *vitro* and that they lose their growth potential both in *vitro* and in *vivo* after incubation with LPS. Differentiation of the leukemia cells was observed in diffusion chambers inserted into the rats given injections of LPS. Injection of LPS inhibited the development of the LPS-sensitive leukemias in syngeneic rats. Moreover, a combined treatment with LPS and daunomycin was able to inhibit the leukemia development completely in all the treated rats bearing LPS-sensitive c-WRT-7 cells. These results suggest that the therapeutic effect of LPS can be ascribed to the induction of "terminal differentiation" of the leukemia cells. It has already been reported that LPS can induce "terminal differentiation" of M1 myeloblastic leukemia cells (12) and that the differentiation of M1 cells can be attributed to the action of differentiation-inducing proteins produced from LPS-stimulated M1 cells (13). Among several macrophage-activating agents, LPS has also been reported to inhibit *in vitro* growth directly without affecting the differentiated functions of several macrophage tumor lines either reversibly (14) or irreversibly (15). In the latter case, LPS-induced growth inhibition is explained by the concept of the induction of "terminal differentiation." Although we have evidence that LPS induces the production of a colony-stimulating factor or colony-stimulating factors from the c-WRT-7 cells as assessed by the colony formation of bone marrow cells in the presence of the conditioned medium of LPS-stimulated c-WRT-7 cells, we have not succeeded in the induction of the differentiation of the c-WRT-7 cells by this conditioned medium alone. Consequently, we regard a direct effect of LPS as a necessary step in the process that induces the differentiation of c-WRT-7 cells. In fact, most of differentiation-inducing agents of c-WRT-7 cells, such as 12-O-tetradecanoylphorbol-13-acetate and OK-432 (penicillin-treated Su strain of *Streptococcus pyogenes*) as well as LPS, are macrophage-activating agents (9). The scanning electron micrographs of LPS-treated c-WRT-7 cells showed characteristic ample ruffles on their surfaces, which are very similar to the enlarged petal-like ruffles observed on the surface of activated macrophages (16). These findings, together with the appearance of la antigens on LPS-treated c-WRT-7 cells, suggest that the process of macrophage activation may be included in the process that induces differentiation.

Little difference was observed in the survival days of the untreated rats, whether they had been given i.p. injections of either the LPS-sensitive or the LPS-hyporesponsive cells. There was, on the contrary, a clear correlation between the *in vitro* effects of LPS on the induction of the differentiation and the *in vivo* inhibitory effects of LPS on the leukemia development. This correlation strongly suggests that the differentiation-inducing action of LPS is responsible for its therapeutic effects. A significant difference in the number of survival days among untreated rats was observed, however, according to the route of administration of the leukemia cells, irrespective of their sensitivity to LPS; rats which had received an i.p. transplantation of the leukemia cells lived significantly longer than those which had received an i.v. transplantation. As we have shown above, small but significant numbers of P2 cells in diffusion chambers implanted into the peritoneal cavity differentiated into macrophage-like cells without any injection of LPS; *in vitro* differen-

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**Table 2** Induction of phagocytic activity in c-WRT-7 P2 cells by various chemotherapeutic drugs

<table>
<thead>
<tr>
<th>Drug</th>
<th>Concentration (ng/ml)</th>
<th>Rate of cell growth (%)</th>
<th>Phagocytic cells <em>a</em></th>
</tr>
</thead>
<tbody>
<tr>
<td>Daunomycin</td>
<td>30</td>
<td>82</td>
<td>1.2</td>
</tr>
<tr>
<td>Daunomycin</td>
<td>60</td>
<td>78</td>
<td>6.0</td>
</tr>
<tr>
<td>Daunomycin</td>
<td>100</td>
<td>25</td>
<td>26.0</td>
</tr>
<tr>
<td>Aclacinomycin A</td>
<td>60</td>
<td>19</td>
<td>24.0</td>
</tr>
<tr>
<td>Vincristine</td>
<td>5</td>
<td>110</td>
<td>1.0</td>
</tr>
<tr>
<td>Actinomycin D</td>
<td>12.5</td>
<td>54</td>
<td>2.9</td>
</tr>
<tr>
<td>Actinomycin D</td>
<td>25.0</td>
<td>19</td>
<td>8.0</td>
</tr>
<tr>
<td>Cycloheximide</td>
<td>40.0</td>
<td>11</td>
<td>2.0</td>
</tr>
<tr>
<td>None</td>
<td>0.15</td>
<td>75</td>
<td>0.3</td>
</tr>
<tr>
<td>None</td>
<td>0.30</td>
<td>67</td>
<td>0.3</td>
</tr>
<tr>
<td>None</td>
<td>0.60</td>
<td>35</td>
<td>1.0</td>
</tr>
<tr>
<td>None</td>
<td>100</td>
<td>0.3</td>
<td>0.8</td>
</tr>
</tbody>
</table>

* *P* < 0.01, compared to Group 4.

---

**Table 3** Inhibition of the development of leukemia by injections of LPS in combination with daunomycin in rats bearing P2S cells

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Group</th>
<th>LPS on day</th>
<th>Daunomycin on day</th>
<th>No. died/used</th>
<th>Mean survival days (range)</th>
</tr>
</thead>
<tbody>
<tr>
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<td>1</td>
<td>0, 1, 2, 3, 4</td>
<td>0, 1, 2</td>
<td>0/5</td>
<td>27.5 (24-34)</td>
</tr>
<tr>
<td>2</td>
<td>2</td>
<td>None</td>
<td>0, 1, 2</td>
<td>4/5</td>
<td>27.3 (23-34)</td>
</tr>
<tr>
<td>3</td>
<td>3</td>
<td>0, 1, 2, 3, 4</td>
<td>None</td>
<td>6/6</td>
<td>25.3 (23-34)</td>
</tr>
<tr>
<td>4</td>
<td>4</td>
<td>None</td>
<td>0, 1, 2</td>
<td>5/5</td>
<td>20.6 (19-22)</td>
</tr>
</tbody>
</table>

* Same in Table 3.

---

**Table 4** Inhibition of the development of leukemia by injections of LPS in combination with daunomycin in rats bearing P2NS cells

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Group</th>
<th>LPS on day</th>
<th>Daunomycin on day</th>
<th>No. died/used</th>
<th>Mean survival days (range)</th>
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</thead>
<tbody>
<tr>
<td>1</td>
<td>1</td>
<td>0, 1, 2, 3, 4</td>
<td>0, 1, 2</td>
<td>6/6</td>
<td>23.7 (21-28)</td>
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<tr>
<td>2</td>
<td>2</td>
<td>None</td>
<td>0, 1, 2</td>
<td>5/5</td>
<td>21.0 (20-23)</td>
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<tr>
<td>3</td>
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<td>0, 1, 2, 3, 4</td>
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<td>6/6</td>
<td>20.0 (18-22)</td>
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<tr>
<td>4</td>
<td>4</td>
<td>None</td>
<td>0, 1, 2</td>
<td>6/6</td>
<td>18.8 (18-20)</td>
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* Same in Table 3.

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* Unpublished data.
tiation of the leukemia cells into macrophage-like cells was accompanied by the retardation of their growth. Accordingly, the longer survival of the leukemia cells in the peritoneal cavity may be due to the partial differentiation of the leukemia cells in that microenvironment. We also suppose that the action of LPS which was so strong as to bring about the cure of a proportion of rats which had received an i.p. transplantation of the leukemia cells can in part be ascribed to a higher susceptibility of the partially differentiating leukemia cells in the peritoneal cavity to the differentiating stimuli by LPS.

Nevertheless, additional studies should be carried out to examine in what way the therapeutic contribution is host mediated. We have evidence that postendotoxin serum has a diated. We have evidence that postendotoxin serum has a

The antileukemia drug daunomycin actually enhanced clearly the therapeutic effect of LPS in rats bearing LPS-sensitive c-WRT-7 cells. It is well established that those agents which inhibit DNA synthesis by a variety of different mechanisms apparently possess a differentiation-inducing action in vitro (17), as we also have shown in the present study. Moreover, several in vitro studies have indicated that various agents which inhibit the synthesis of DNA by various mechanisms are able to increase the degree of differentiation of the leukemia cells in combination with differentiation inducers (18-21).

In this context, we presume that this successful outcome of the combination therapy in the LPS-sensitive leukemia is due not only to an effective reduction of the tumor burden by daunomycin to an amount on which LPS alone can work but also to a combined effect of LPS and daunomycin on the promotion of the in vivo differentiation of the leukemia cells. However, the effect of combined treatment with LPS and daunomycin on the LPS-hyporesponsive leukemia was minimal. Another approach, for example, using actinomycin D as a sensitizer to differentiation inducer (22) may be useful.

Our results thus indicate the possibility of controlling differentiation-sensitive leukemia cells by the administration of a differentiation inducer, especially if this is associated with the administration of a chemotherapeutic agent. Although it is unlikely that the results obtained with the c-WRT-7 leukemia can be extrapolated to cover the majority of primary human myeloid leukemia, our results and those of others (23-25) clearly indicate that phenotypic changes of leukemia cells may be brought about in vivo, thus leading to a possible elimination of the growth potential of leukemia cells. Consequently, we propose that an approach using in vivo interaction of a biological agent and a chemotherapeutic agent may be worth further investigation.

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REFERENCES

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