Response of a Transplantable Lymphosarcoma to Colchicine

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Many attempts have been made to cure experimental tumors or human malignant growths with colchicine. In 1941, Ludford (1) concluded that colchicine produces "complete regression of some tumors, but only by employing large doses of the drug just below the minimum lethal dose." Lits, Kirschbaum, and Strong (2), using a transplantable lymphosarcoma in mice, found that colchicine would apparently cause complete regression in some animals but that recurrence inevitably occurred. One of the most successful attempts in treating a transplanted lymphosarcoma was reported by Heilman and Kendall (3). They showed that Compound E (11-dehydro-17-hydroxycorticosterone) produced complete regression in some mice bearing a transplantable lymphosarcoma; however, in most animals regression was not complete or if complete was only temporary. Bass and Feigelson (4) demonstrated that colchicine is more effective than nitrogen mustard or urethan in producing acute regression of 6C3HEDA tumors in mice. In these studies, tumor regression was invariably observed following colchicine administration. The object of the present study was to extend these observations and to investigate the effects of prolonged administration of colchicine on this tumor.

MATERIALS AND METHODS

A 6C3HEDA lymphosarcoma originally obtained from Dr. W. U. Gardner was used. This tumor has been carried through repeated transplantations in our laboratory for the past 3 years. It does not regress spontaneously, and only rarely is a transplantation unsuccessful. It is, therefore, highly satisfactory for studying chemotherapeutic agents. Without therapy the tumor-bearing mice live 18-21 days. All animals were fed Purina Dog Chow and given water ad libitum. C3H or C3H F1 hybrid mice 6-12 weeks old were used. Initial tumor transplantation was made with a 15-gauge needle. Small pieces of tumor were placed subcutaneously in the region of the right axilla. Tumor size was measured at frequent intervals.

Colchicine U.S.P. dissolved in distilled water was administered intraperitoneally. Treatment (unless otherwise stated) was begun when the tumor measured approximately 1 cm. in diameter (8-14 days after implantation). For comparison, ethyl carbamate and cortisone were also employed. Ethyl carbamate (urethan) was administered intraperitoneally, cortisone (cortisone acetate in saline suspension), subcutaneously.

RESULTS

The results obtained are shown in Table 1.

When tumor-bearing C3H F1 hybrid mice were treated with colchicine (0.75 mg/kg) daily for a period of 23 days (Group 1), the transplanted tumors steadily regressed until they entirely disappeared in from 4 to 9 days. Animals so treated were observed for a period of 150 days without showing evidence of recurrence. These animals were then the recipients of a second transplant, made in the region of the original implant. In a few instances, small nodules developed which rapidly regressed; their nature was not investigated. A third transplant was then made on the left side, opposite the site of the original transplant, following which there was no evidence of tumor growth.

In a group of nine mice receiving a smaller dose of colchicine (0.5 mg/kg) for the same period of time, complete regression of the implanted tumor occurred in four animals. Reinoculation at the site of the original implant resulted in the appearance on about the eighth day of small nodules which entirely disappeared by the thirteenth day. When the transplantation was repeated on the opposite side of each animal, no evidence of a take was observed.

A third group of ten animals was selected for a shorter period of therapy. The animals were given a daily colchicine dose of 0.5 mg/kg which was increased to 0.75 mg/kg if the tumor failed to regress. The total period of treatment varied from 5 to 9 days. All tumors regressed. On the 94th day, and again on the 124th day, after the initial transplantation attempts to obtain new takes of the same tumor with the procedure described in the preceding paragraph were unsuccessful.
To a fourth group of twenty CSH mice colchicine (0.75 mg/kg) was administered daily for 3 days. In twelve animals the tumor showed complete regression; these animals were not receptive to the tumor 46 days following the original implantation.

To exclude the possibility that the age of the animal might be a factor in the failures obtained on the second and third transplantations, fresh tumor fragments were implanted in the right axilla of six 7-month-old normal mice. Takes were obtained in all six animals.

The results from a 2-day course of therapy are shown in Table 1, Group 5. Out of 28 C3H F1 hybrid mice so treated, ten tumors regressed and did not recur during a 3-month period of observation.

DISCUSSION

Immunity following chemical cure of a tumor with colchicine has been reported by Peyron, LaFay, and Klobzieff (5), who used the Shope rabbit papilloma. Cured rabbits were immune to the virus. The development of antibodies in mouse leukemia has been reported by Furth (6) and Gorer (7). The recent observations of Stoerk and Emerson (8) show that riboflavin deficiency causes permanent suppression of the 6C3HED tumors associated with the development of immunity, whereas pyridoxine-deficient animals show tumor suppression only while the therapy is continued. This is interpreted by the authors as a failure of immunity to develop under the conditions of the latter experiment.

<table>
<thead>
<tr>
<th>Group</th>
<th>Treatment</th>
<th>Strain of mice</th>
<th>Permanent complete regression</th>
<th>Treatment deaths</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>colchicine 0.75 mg/kg daily for 23 days</td>
<td>C3H F1 hybrid</td>
<td>8/10</td>
<td>2/10</td>
</tr>
<tr>
<td>2</td>
<td>colchicine 0.5 mg/kg daily for 23 days</td>
<td>C3H F1 hybrid</td>
<td>4/9</td>
<td>0/9</td>
</tr>
<tr>
<td>3</td>
<td>colchicine 0.5 mg/kg daily for 5-9 days, varying with tumor response</td>
<td>C3H F1 hybrid</td>
<td>10/10</td>
<td>0/10</td>
</tr>
<tr>
<td>4</td>
<td>colchicine 0.75 mg/kg daily for 3 days</td>
<td>C3H F1 hybrid</td>
<td>18/20</td>
<td>3/20</td>
</tr>
<tr>
<td>5</td>
<td>colchicine 0.75 mg/kg daily for 2 days</td>
<td>C3H F1 hybrid</td>
<td>10/28</td>
<td>1/28</td>
</tr>
<tr>
<td>6</td>
<td>none</td>
<td>CSH</td>
<td>0/20</td>
<td>0/20</td>
</tr>
<tr>
<td>7</td>
<td>none</td>
<td>CSH F1</td>
<td>0/8</td>
<td>0/8</td>
</tr>
<tr>
<td>8</td>
<td>urethan 100 mg/100 gm body weight daily 8 days</td>
<td>CSH</td>
<td>1/18</td>
<td>9/18</td>
</tr>
<tr>
<td>9</td>
<td>urethan 8 mg daily for 4 days</td>
<td>CSH</td>
<td>0/8</td>
<td>5/8</td>
</tr>
</tbody>
</table>

* Mice were approximately 8 months of age at time of transplantation. Mice were all dead by 92d day.
† Mice were approximately 9 months of age at time of transplantation. Mice were all dead by 94d day.

The present results indicate that 6C3HED tumors in C3H mice regress completely and apparently permanently when the animals are treated with appropriate doses of colchicine. Although the number of treated animals studied in each group is not large, the results appear significant, since none of the untreated controls regressed. Moreover, our experience with the tumor in the past 4 years has shown that no tumor regression has occurred in healthy animals. It is possible that the difference in results here reported from those of Lits, Kirschbaum, and Strong (2) may occur because of the treatment schedule employed, the strain of mouse used, or some specific characteristic of the tumor. The failure of cortisone, under the conditions of this experiment, to produce permanent regression would strongly suggest that the "tumorolytic" action of colchicine is not on the basis of an "alarm reaction" but rather a direct effect of the agent on tumor tissue.

CONCLUSIONS

It has been shown that colchicine administration produces permanent regression of lymphoma 6C3HED. Evidence is presented which strongly
indicates that the colchicine acts directly on the malignant lymphoid tissue.

An immunity to this tumor developed after regression of the initial implant. This immunity developed before the 46th day and persisted to at least the 173d day after original transplantation was made.

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REFERENCES

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