New Chemotherapeutic Agents in Hodgkin’s Disease

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Summary

There is a need for new agents and drug combinations in the treatment of Hodgkin’s disease.

Several interesting new agents have been introduced into each of the conventional categories of tumor drugs, including streptonigrin and etiocholanolone. The relative lack of use of some of the older antimetabolites and sex steroids is due for re-examination. This may shed light on a rational basis for choosing agents to use on cell types with long life-spans and low mitotic rates.

There is a need for preclinical pharmacologic information on animal tumors which more closely resemble human lymphoproliferative tumors in terms of long life-span of the cell, marked and acquired resistance to alkylating agents.

High dose corticoid therapy in Hodgkin’s disease appears to be more effective than in acute leukemia and should be more widely used. The substituted vinca alkaloids have shown practical and theoretical promise in dealing with the difficult phenomenon of acquired drug resistance. The methylhydrazine derivative, ibenzzmethyazine, represents a new class of effective agents.

Combination therapy has demonstrated effectiveness in prolonging remissions and there are theoretical reasons to investigate the possibility of prolonging remissions even further by such methods.

Introduction

Although there are 4 or more agents now in general use which are highly effective in the treatment of Hodgkin’s disease, at present no one agent is curative for the disease and there is general agreement that new and better agents are still needed. It can be taken as axiomatic that when 4 agents are in use, no single agent is highly effective both in inducing and maintaining remissions.

The major persisting problems that stimulate the search for better agents are lack of understanding of etiology, uncertainty concerning pathogenetic mechanisms, incompleteness of responses, and the development of resistance. In order to seek out or design an agent which will directly attack any of these problems, more fundamental knowledge is needed than is currently available. Animal screens have helped to select effective agents with a fair degree of predictability for the human disease. Such screens have not been studied sufficiently at the cellular level to enable us to understand the pharmacologic basis for drug action. For example, many of the transplanted lymphocytic tumors used in the screen have rapid mitotic rates and short division times and are sensitive to antimetabolites. These cells may not be optimally comparable to human lymphoproliferative diseases which seem to involve long-lived, slowly dividing lymphocytes which are not so sensitive to antimetabolites. A different and more useful type of screening data might come out of the use of some slow-growing rodent lymphomas.

Alkylating Agents

The ones under trial are for the most part derivatives of current compounds (Table 1). In previously untreated diseases, the responses are about as frequent as those reported for other members of the mustard family. The qualitative differences in the antileukemic effect between cyclophosphamide and other nitrogen mustards has reemphasized the possibility of finding an alkylating agent which will be considerably more effective in Hodgkin’s disease than the current ones. The superior effect of all alkylating agents upon lymphocytes and in most lymphoproliferative malignancies and the differential effects of the methanesulfonate upon granulocytes need more study at the cellular pharmacologic level.

Antimetabolites (Table 2)

The use of antimetabolite agents in the treatment of lymphoma has been infrequent, and the results are scant, and on the average, unimpressive. In this sense they are “old” drugs not currently under study. However, the reasons for their lack of effect might, if better understood, allow modifications of the method of administration which would give them a “new look.”

The early successful use of these agents in acute leukemia may have led to their premature discontinuation since solid tumor responses were much less frequent. A response rate of 25% in Hodgkin’s disease for the antifols has been reported since their introduction, but recent studies with different methods of drug administration may permit higher responses to be achieved. The antipyrimidines and antipurines have been only superficially studied in the lymphomas, and a true response rate has yet to be established. Since the life-span of a lymphocyte is apparently much longer than that of a granulocyte, the division time may also be very long and the use of antimetabolites may be, pari passu, less effective than in the case of more rapidly dividing cells which have a complete complement of the target enzymes involved in nucleic acid biosynthesis. Data from our laboratory indicate that in the case of 5-fluorouridine and 6-mercaptopurine, which must be metabolized to nucleotides before they pass in vivo, less effective than in the case of more rapidly dividing cells which have a complete complement of the target enzymes involved in nucleic acid biosynthesis.
might be rendered more sensitive to the action of antimetabolites. Presently studying some methods by which the cells involved metabolise, is absent from Hodgkin’s disease tissues. We are atate synthetase, the target enzyme for the halopyrimidine anti-

Roberts, unpublished data). We have also found that thymidyl-

lymphocytic leukemia (49) and lymphoma (T. C. Hall and B. D.

metabolised and retained as the nucleotides within the cell. Folie reducéase has been found missing from the cells of chronic

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cytolymphatic (lymphosarcoma) (15, 32). At the doses usually employed, 30-60 mg of
corticoids were found quite effeciive in acule lymphatic leu

carcinoma, was undertaken in use of much higher “pharmacologie” doses, comparable to the

prednisone equivalent, there was also an obvious beneficial effect seen in the hemolytic process seen in cancer of the breast. The

upon the hemolytic anemia of lymphoma. This effect is also seen in leukemia (43) and somewhat effective in chronic lymphocytic

cancer, was undertaken in

these drugs, which enter the cells by passive diffusion, are not metabolised and retained as the nucleotides within the cell. Folic

reductase has been found missing from the cells of chronic lymphocytic leukemia (49) and lymphoma (T. C. Hall and B. D.

Roberts, unpublished data). We have also found that thymidylate synthetase, the target enzyme for the halopyrimidine antime

Table 1

<table>
<thead>
<tr>
<th>Agent</th>
<th>Reported response</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dopan</td>
<td>“Good”</td>
<td>25</td>
</tr>
<tr>
<td>Alanine mustard</td>
<td>2/4</td>
<td>8</td>
</tr>
<tr>
<td>Trenimon</td>
<td>9/13</td>
<td>27</td>
</tr>
<tr>
<td>Degranol</td>
<td>19/24</td>
<td>51</td>
</tr>
<tr>
<td>Mannitol mustard</td>
<td>6/6</td>
<td>11</td>
</tr>
<tr>
<td>R-49</td>
<td>10/21 (3 complete)</td>
<td>10</td>
</tr>
<tr>
<td>R-49</td>
<td>6/8</td>
<td>18</td>
</tr>
<tr>
<td>R-49</td>
<td>9/14</td>
<td>19</td>
</tr>
<tr>
<td>N-Formyl sarcosine</td>
<td>11/13</td>
<td>58</td>
</tr>
</tbody>
</table>

Table 2

<table>
<thead>
<tr>
<th>Agent</th>
<th>Responses reported</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>6-Mercaptopurine</td>
<td>1/11</td>
<td>53</td>
</tr>
<tr>
<td>Cytosine arabinoside</td>
<td>“Definite regressions”</td>
<td>35</td>
</tr>
<tr>
<td>5-Fluorouridine</td>
<td></td>
<td>Miller*</td>
</tr>
<tr>
<td>Methotrexate</td>
<td>2/4</td>
<td>14</td>
</tr>
<tr>
<td>Dichloromethotrexate</td>
<td>2/5 + 3/6 = 5/11</td>
<td>14</td>
</tr>
</tbody>
</table>

* Survey of literature references provided through the courtesy of Dr. Edward Miller, Hoffman-La Roche.

Table 3

<table>
<thead>
<tr>
<th>Antibiotics in Hodgkin’s Disease</th>
<th>Reported response rate</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Actinomycin D</td>
<td>4/4 (1 dramatic) (Burkitt’s tumor)</td>
<td>42</td>
</tr>
<tr>
<td>Actinomycin C</td>
<td>9/14</td>
<td>9</td>
</tr>
<tr>
<td>Actinomycin C</td>
<td>13/19</td>
<td>40</td>
</tr>
<tr>
<td>Mitomycin C</td>
<td>1/2</td>
<td>13</td>
</tr>
<tr>
<td>Mitomycin C</td>
<td>0/3</td>
<td>4</td>
</tr>
<tr>
<td>Mitomycin C</td>
<td>5/13</td>
<td>23</td>
</tr>
<tr>
<td>Mitramycin</td>
<td>2/2 (slight)</td>
<td>28</td>
</tr>
<tr>
<td>Mitramycin</td>
<td>0/1</td>
<td>55</td>
</tr>
<tr>
<td>Streptonigrin</td>
<td>3/3 (lymphosarcoma)</td>
<td>56</td>
</tr>
<tr>
<td>Streptonigrin (CH₃ ester)</td>
<td>6/9</td>
<td>22</td>
</tr>
<tr>
<td>Streptonigrin (CH₃ ester)</td>
<td>9/15</td>
<td>48</td>
</tr>
<tr>
<td>Olivomycin</td>
<td>2/2</td>
<td>38</td>
</tr>
<tr>
<td>Chrysomallin</td>
<td>5/7</td>
<td>38</td>
</tr>
<tr>
<td>Aurantin</td>
<td>26/40</td>
<td>45</td>
</tr>
<tr>
<td>No. 2703</td>
<td>5/5 (2 complete)</td>
<td>31</td>
</tr>
<tr>
<td>Actinomycin C</td>
<td>41/92</td>
<td>2</td>
</tr>
<tr>
<td>Actinomycin C</td>
<td>26/44</td>
<td>39</td>
</tr>
</tbody>
</table>

Drug induction of folic reductase in malignant lymphocytes has not been possible to date (42). We are currently beginning to study the changes in enzymatic pattern and drug metabolism induced in vivo by phytohemagglutinin. Such changes might be useful in inducing a state of antimetabolite sensitivity.

Antibiotics (Table 3)

These products represent the bulk of materials studied in the ongoing empiric search for new agents. Because they are produced in large numbers, and the number of human patients on whom they can be tried early is finite, the need is great both for an understanding of their cellular pharmacology and for an improved animal screening system which will predict for antitumor response in man. In addition to the drug-sensitive tumors now in use, a group of alkylating agent-resistant tumors would be very helpful in screening for agents which might be useful in patients who had failed to respond to or relapsed on mustards. The studies which have been made of the mechanism of action indicate that most of these agents have direct and powerful effects upon nucleic acids. Mitomycin C and streptonigrin have been suggested to act as biologic alkylating agents.

The indication that nucleic acids may be drug sensitive and the life of the lymphoid cell dependent upon them even though it may not be dividing opens an area for potential useful therapeutic investigation. There are a large number of antibiotics under study outside of the United States, particularly in Japan and Eastern Europe, which might profitably be the subject for international collaboration. Many of them are devoid of myelosuppressive effects and might be of interest in patients with advanced disease and leukopenia.

Streptonigrin and its methyl ester are the most promising of the newly available antibiotic compounds; the former is already undergoing a double-blind comparison with chlorambucil in the Veterans Cooperative Group. Actinomycin C and mitomycin C have never received an adequate trial in this country. They should probably be reexamined in a total of at least 25 patients. Promising new antibiotics should have at least this number of clinical trials before being discontinued, and some trials should be made in patients who have indolent early Stage III disease, since we may miss valuable information about new drugs if they are always restricted to initial use in patients who are resistant to conventional therapy.

Steroids (Table 4)

The antilymphatic and thymolytic actions of corticoids led naturally to their early use in lymphoproliferative diseases. Since there is much evidence of a natural interrelationship between lymphoid apparatus and hormone production of several types, this area was one of interest because lymphoma control might be closely related to normal physiologic mechanisms. The corticoids were found quite effective in acute lymphatic leukemia (43) and somewhat effective in chronic lymphocytic leukemia (15, 32). At the doses usually employed, 30-60 mg of prednisone equivalent, there was also an obvious beneficial effect upon the hemolytic anemia of lymphoma. This effect is also seen in the hemolytic process seen in cancer of the breast. The use of much higher “pharmacologic” doses, comparable to the high steroid doses used in breast cancer, was undertaken in

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TABLE 4
STEROIDS IN HODGKIN’S DISEASE

<table>
<thead>
<tr>
<th>Agent</th>
<th>Responses reported</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adrenocorticotropic hormone</td>
<td>4/6</td>
<td>43</td>
</tr>
<tr>
<td>and cortisone</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prednisone (low dose)</td>
<td>2/21</td>
<td>17</td>
</tr>
<tr>
<td>Prednisone or prednisolone</td>
<td>10/10</td>
<td>46</td>
</tr>
<tr>
<td>Medrol (high)</td>
<td>19/35</td>
<td></td>
</tr>
<tr>
<td>Prednisolone (high)</td>
<td>28/53</td>
<td>29</td>
</tr>
<tr>
<td>Etiocholanolone</td>
<td>4/7 (all types of lymphoma)</td>
<td>20</td>
</tr>
</tbody>
</table>

TABLE 5
HIGH DOSE CORTICOSTEROIDS IN LYMPHOMA

| Total patients evaluated     | 35      |
| Number with Hodgkin’s        | 25      |
| Total responses              | 19      |
| Objective changes            |         |
| Shrinkage of nodes           | 19/31   |
| Clearance of edema           | 4/4     |
| Resorption of pleural fluid  | 4/6     |
| Rise in Hb > 1 gm            | 21/32   |
| Relief of pruritis           | 3/6     |
| Median time to onset of response | 2 wk. |
| Duration of response (wk.)   | 2-60, median 10, mean 15 |

* More than 45 mg of prednisone daily for more than 3 wk.

Acute leukemia and proved rather ineffective (46, 52). The use of high-dose corticoids in Hodgkin’s disease has not been so well studied or reported, and is generally stated to be of little use. We have undertaken such a study with rather interesting results. We treated 54 patients with lymphoma, who were resistant to other forms of therapy, with high doses of corticoids. Thirty-five of these received initial daily doses of 45-1000 mg of prednisone or equivalent, for at least 3 weeks. Nineteen of these patients achieved definite, objective remissions. These lasted from 2 to 60 weeks, with a median duration of 10 weeks and a mean duration of 16 weeks. This is the same remission duration reported for benzamethazine. The character of the responses is shown in Table 5. The side effects encountered with the high doses of corticoids involved were late in onset and well tolerated (Table 6). No drug-associated deaths were encountered, and hyperglycemia was easily controlled with oral antidiabetic preparations or small doses of insulin. All patients with gastrointestinal discomfort or bleeding responded to diet and antacids. These results are suggestive of a direct antitumor effect for the corticoids, which may be of some value in clinical management of the advanced patients.

TABLE 6
HIGH DOSE CORTICOSTEROIDS—SIDE EFFECTS

<table>
<thead>
<tr>
<th>Infection</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bacterial</td>
<td>5</td>
</tr>
<tr>
<td>Monilial</td>
<td>4</td>
</tr>
<tr>
<td>Hyperglycemia (mild)</td>
<td>7</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td></td>
</tr>
<tr>
<td>Pain</td>
<td>5</td>
</tr>
<tr>
<td>Bleeding</td>
<td>2</td>
</tr>
<tr>
<td>Soft tissue</td>
<td></td>
</tr>
<tr>
<td>Acne</td>
<td>6</td>
</tr>
<tr>
<td>Moonface</td>
<td>9</td>
</tr>
<tr>
<td>Hirsutism (female)</td>
<td>1</td>
</tr>
<tr>
<td>Central nervous system—transient psychoses</td>
<td>3</td>
</tr>
</tbody>
</table>

* Thirty-five patients.

Miscellaneous Agents (Table 7)

The vinca alkaloids have been the most effective agents introduced during the past several years. Velban has achieved a definite 2nd place in the management of Hodgkin’s disease. At present, the status of vincristine is less clear, with some indications that, although active, it may be less effective in Hodgkin’s disease. The results of the current protocol studies will be of help in clarifying this. There are a number of other natural vinca alkaloids, such as vinleurosine and vinrosidine, which have not been shown to have antilymphoma activity equal to that of Velban, and at present none have been studied extensively. Desacetyl vinblastine 4-(N,N-dimethylaminoacetate) sulfate is the 1st of a series of modified vinblastines to undergo drug areas that most needs increased attention in both biochemical and clinical pharmacology.

The marked susceptibility of normal and malignant lymphoid tissue to the action of corticoids has been attributed to effects on cell membranes. If this is indeed a primary locus of cytotoxic action in rather slowly dividing cells, many of the concepts relating cell-killing effect and division times may have to be revised.
clinical trial. Given i.v. weekly it has apparently no cross reactivity with the parent drug or with vincristine. It also seems to be active orally. This suggestion that resistance to Velban may not be associated with resistance to the antitumor part of the molecule may be a step forward in helping to understand and control the development of resistance. Demeocolin is another plant alkaloid which has been available for years, and which is generally not thought of as a drug of use in Hodgkin's disease. Its mode of action, and may be additive. The versatility of the Hodgkin's number of effective drugs which may have different modes of action, and may be addictive. The versatility of the Hodgkin's cell in developing drug resistance to all currently available agents might be circumvented by drug combinations. Hence, destruction of all the cells in Hodgkin's disease may likely result in cure, and anything less than complete destruction will surely result in ultimate relapse (54). The difficulties with the multiple therapy approach are also formidable—all of the agents are myelosuppressive, all impair the immunologic responses of the host, and many are in themselves carcinogenic in animals.

The 1st combinations used involved X-ray therapy plus nitrogen mustard, and although cures were not found, Karnofsky and co-workers seemed to have significantly prolonged the duration of response in their series (Table 9). Massive doses of prednisone plus X-ray therapy have been employed by Kaplan and his associates, with initially promising results. The combination of vincristine, prednisone, cytoxan, and methotrexate with or without radiation therapy as used by the National Cancer Institute group has apparently also resulted in major prolongation of unmaintained remissions to 16 months in all but 2 of the patients in the series.

**Drug Combinations**

The existence of a 70% 5-year survival rate after the surgical removal of localized Stage I lymphoma may be taken as presumptive evidence of an early localized and curable phase of the disease (33). The "curative" use of intensive local radiotherapy reinforces this concept (44). Combination therapy for more extensive disease is attractive because of the existence of a number of effective drugs which may have different modes of action, and may be additive. The versatility of the Hodgkin's disease is still under study and awaits comparative trials with standard agents. Three areas of interest and concern are the reports of a high degree of carcinogenicity in rodents, a potent myelosuppressive capacity, and the central nervous system manifestations of depression and somnolence.

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**TABLE 9**

**COMBINATION THERAPY IN HODGKIN'S DISEASE**

<table>
<thead>
<tr>
<th>Agents</th>
<th>Dose</th>
<th>Responses reported</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>X-ray +</td>
<td>4000 r between chemotherapy</td>
<td>13/14 + prolonged remission</td>
<td>7</td>
</tr>
<tr>
<td>Cytoxan</td>
<td>600 mg/sq m/wk.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vincristine +</td>
<td>1.2 mg/sq m/wk.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Methotrexate +</td>
<td>30 mg/sq m/twice weekly</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prednisone.</td>
<td>40 mg/sq m/day</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HN2 + X-ray</td>
<td>0.4 mg/kg 2500-3000 r</td>
<td>8/13 surviving 5–14 yr. (Stages 1, 2)</td>
<td>24</td>
</tr>
<tr>
<td>Vinblastine + Chlorambucil</td>
<td>0.1 mg/kg wk. 4 mg/day</td>
<td>13/16 (prolonged remissions, mean 7.5+ mo.)</td>
<td>34</td>
</tr>
</tbody>
</table>

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**TABLE 8**

**EFFECTIVENESS OF IBENZMETHYZINE IN HODGKIN'S DISEASE**

<table>
<thead>
<tr>
<th>Reference</th>
<th>Responses reported</th>
<th>Median duration</th>
<th>Toxicity</th>
</tr>
</thead>
<tbody>
<tr>
<td>5</td>
<td>12/20</td>
<td>4 mo.</td>
<td>+ + +</td>
</tr>
<tr>
<td>36</td>
<td>25/25</td>
<td>75 days</td>
<td>+ + +</td>
</tr>
<tr>
<td>37</td>
<td>39/51</td>
<td>2–7 mo.</td>
<td>+ + +</td>
</tr>
<tr>
<td>16</td>
<td>4/7</td>
<td></td>
<td>+ + +</td>
</tr>
<tr>
<td>26</td>
<td>13/20</td>
<td></td>
<td>+ +</td>
</tr>
<tr>
<td>57</td>
<td>15/24</td>
<td>3.3 mo.</td>
<td>+ +</td>
</tr>
<tr>
<td>12</td>
<td>12/13</td>
<td>4 mo.</td>
<td>+ +</td>
</tr>
</tbody>
</table>

The methylhydrazine derivative, ibenzmethyzine, or Natulan, is the most interesting newcomer in the area of uncategorized agents which are useful in Hodgkin's disease. Its mode of action is not known; it has been suggested to release H₂O₂ or to undergo an in vivo conversion to an alkylating agent. Table 8 summarizes some of the reports in the literature about the agent. It seems to have no cross resistance with other agents, and to induce remissions of good quality with respectable frequency. Its ultimate place in the management of Hodgkin's disease is still under study and awaits comparative trials with standard agents. Three areas of interest and concern are the reports of a high degree of carcinogenicity in rodents, a potent myelosuppressive capacity, and the central nervous system manifestations of depression and somnolence.
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