INTRODUCTION

Vincristine (Oncovin, Eli Lilly Co., Indianapolis, Ind.) is a dimeric alkaloid similar in structure to vinblastine, substituting only a formyl group for the methyl radical of vinblastine. It was recognized as a candidate compound of potential interest for human cancer by Johnson et al. (6) because it produced indefinite survivors in mice bearing P1534 leukemia, AKR leukemia, B82 leukemia, and Sarcoma 180. Initial studies in man by Armstrong et al. (1) recorded evidence of drug activity in patients with lymphosarcoma, Hodgkin's disease, and astrocytoma. These observations were extended by Costa et al. (4), who recognized tumor regressions in patients with a wide variety of neoplasms.

The studies here reported were conducted over 21 months starting in December 1961 by the Eastern Cooperative Oncology Group (formerly Eastern Solid Tumor Group) to assess the clinically useful spectrum of activity of vincristine in neoplastic disease. The data have since been used by Group investigators in the formulation of combination chemotherapy programs. No similarly extensive data have been reported for the drug used alone, and the data are thus communicated despite the evolution of methodology and critique in the intervening decade.

MATERIALS AND METHODS

Patients with all types of metastatic cancer were included in the experimental design of the study. It was required that their neoplasm be advanced and unsuitable for curative surgery or radiation, that it show evidence of progression, and that at least some neoplastic lesions be measurable by palpation or X-rays. Where exact measurement was impossible, the tumor had to be such that a 50% reduction in mass could be estimated.

Patients were considered "good risk" if on entry to the study they had an estimated survival of at least 2 months, a leukocyte count over 5,000/cu mm, and a platelet count greater than 100,000/cu mm. In addition, good-risk patients could show no evidence of azotemia (blood urea nitrogen less than 20 mg/100 ml or nonprotein nitrogen less than 30 mg/100 ml) or any residual toxic or beneficial effect from prior chemotherapy. All patients who failed to qualify for these parameters were classified "poor risk."
sidered poor risk because of the possibilities of cross-resistance and of cumulative toxicity.

In the 1st study design, all patients were given 75 μg/kg/week. After 4 months, the protocol was modified, and random allocation to 75 or 50 μg/kg/week was prescribed. When therapeutic responses occurred at 50 μg/kg/week, a search for a lower effective dose was made by randomization between 50 and 25 μg/kg/week. Tumor responses in patients with breast cancer and lymphomas seemed diminished by the decrease in dose, and an additional group of patients with these diseases was randomized between doses of 25 and 12.5 μg/kg. All drug doses were given by rapid i.v. injection, often through the tubing of a running infusion to avoid paravasous infiltration.

Partial regression of measured tumor was considered to begin when the average tumor size, determined by the product of the 2 maximum perpendicular diameters of all measured lesions, decreased to 75% or less of the pretreatment level. Complete regression was defined as no evidence of residual disease. In patients with palpable but not measurable disease, a regression required decrease by 50% or more in 1 diameter. Unequivocal growth of a single lesion, regardless of the change in remaining lesions, disqualified the regression. The decrease in size of a partial or complete regression had to persist for at least 2 consecutive measurements. Relapse began when the product of the diameters of a measured tumor mass, observed over 2 consecutive measurement periods, increased by 50% over that which had been obtained at maximum response and exceeded 2 sq cm, or when new lesions appeared. Survival curves were plotted by the life table technique.

A schedule of downward modifications of drug dose was related to hematological toxicity. A full dose was given for leukocyte counts above 5,000/cu mm. The dose was decreased by 25% of the original dose for each fall of 1,000 leukocytes/cu mm in peripheral count. For leukopenia at 2,000/cu mm or less, no drug was given. A platelet count of less than 100,000/cu mm called for a 50% decrease in dose, with omission of drug if the platelet count fell to less than 75,000/cu mm.

Paresthesias limited to hands and feet were extremely common and, when not progressive, did not mandate discontinuation of drug administration. If progressive neuropathy appeared, drug was omitted or decreased until toxicity cleared.

A provision was incorporated to raise drug dose to the next higher level after 4 weeks of treatment if no toxicity or tumor regression was seen. The study terminated at any time after the 4th week that toxicity and tumor progression coexisted, when relapse followed regression, or if toxicity had appeared by the 8th week without evidence of tumor regression. Upon admission and at stated intervals during the study, medical, laboratory, and radiological surveillance was prescribed. The drug was generously provided in 1-mg ampuls by Dr. James Armstrong of Eli Lilly Co.

After reviewing the charts of the 1st 212 patients, a toxicity classification was adopted which was:

Grade 1 Mild. Mild weakness, paresthesia, myalgia, jaw, throat, or bone ache, insomnia, numbness, tingling, constipation, alopecia, leukopenia to 2000/cu mm, thrombocytopenia.

Grade 2 Moderate. Slapping gait or foot drop, wrist drop, severe weakness, laryngeal paralysis, extraocular motor palsy, abdominal pain (Grade 2 or more), generalized pain, mild atrophy, inability to write or button, mild confusion, leukopenia less than 2000/cu mm, thrombocytopenic bleeding.

Grade 3 Severe. Atrophy, inability to walk, persistent wrist or foot drop, ileus requiring tube or surgery, psychosis, disorientation, hallucinations, paralysis.

Grade 4 Fatal.

RESULTS

A total of 407 patients were entered on the study. Fifteen were invalidated for procedural errors, leaving 392 evaluable patients. Each of the 9 institutions contributed from 28 to 65 patients with 0 to 10% disqualification rates. The interinstitutional distribution was comparable over the 4 dose ranges as was the proportion of patients qualified as good risk, 49 to 69%, with the exception of a single institution with the lowest case contribution where good risk constituted only 39%.

The 6 most responsive tumor types were Hodgkin's disease, lymphosarcoma, reticulum cell sarcoma, carcinoma of the breast, carcinoma of the bladder, and carcinoma of unknown primary site. The last 2 types had small numbers of patients. For each of the other 4 neoplasms, the response rate in patients classified as good risk was superior to those in the poor risk category (Table 1). The response rates in these 4 disease types were not clearly related to the initial prescribed dose, doubtless in part related to augmentation of decrease of dose level. Indeed, for the 4 tumor types, the best results occurred at each of the 4 different dose levels, 75, 50, 25, or 12.5 μg/kg/week. The number of patients with each disease at each dose is small, however, and is influenced by risk status. A "total drug activity" assessment by dose, lumping the 4 neoplasms at the different dose levels, showed a nearly identical response rate of from 34 to 41%. The composite response rates for the 3 lymphomas (37 to 50%) appear better than that for breast cancer (24%). Additional types of advanced cancer were studied without finding clinically important effectiveness (Table 2). Among good-risk patients the response rate was

<table>
<thead>
<tr>
<th>Tumor type</th>
<th>Patients</th>
<th>Response*/total patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hodgkin's disease</td>
<td>41</td>
<td>14/22 (64%) 6/19 (32%)</td>
</tr>
<tr>
<td>Lymphosarcoma</td>
<td>26</td>
<td>10/17 (59%) 3/9 (33%)</td>
</tr>
<tr>
<td>Reticulum cell sarcoma</td>
<td>24</td>
<td>7/16 (44%) 2/8 (25%)</td>
</tr>
<tr>
<td>Carcinoma of breast</td>
<td>62</td>
<td>11/34 (32%) 4/28 (14%)</td>
</tr>
</tbody>
</table>

* Complete plus partial response.
Response of various tumors by dose and risk category to vincristine treatment of patients with advanced neoplasms

<table>
<thead>
<tr>
<th>Tumor type</th>
<th>Total</th>
<th>Response/total</th>
<th>75 µg</th>
<th>50 µg</th>
<th>25 µg</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Good risk</td>
<td>Poor risk</td>
<td>Good risk</td>
<td>Poor risk</td>
</tr>
<tr>
<td>Carcinoma of lung</td>
<td>37</td>
<td>1/18</td>
<td>1/19</td>
<td>0/13</td>
<td>1/12</td>
</tr>
<tr>
<td>Melanoma</td>
<td>26</td>
<td>2/17</td>
<td>1/9</td>
<td>1/8</td>
<td>0/2</td>
</tr>
<tr>
<td>Carcinoma of head and neck origin</td>
<td>25</td>
<td>1/19</td>
<td>0/6</td>
<td>0/14</td>
<td>0/3</td>
</tr>
<tr>
<td>Carcinoma of ovary</td>
<td>17</td>
<td>0/5</td>
<td>0/12</td>
<td>0/2</td>
<td>0/8</td>
</tr>
<tr>
<td>Carcinoma of unknown primary site</td>
<td>15</td>
<td>3/9</td>
<td>2/6</td>
<td>1/5</td>
<td>1/4</td>
</tr>
<tr>
<td>Sarcomas</td>
<td>14</td>
<td>2/8</td>
<td>0/6</td>
<td>0/1</td>
<td>0/1</td>
</tr>
<tr>
<td>Carcinoma of cervix</td>
<td>13</td>
<td>1/8</td>
<td>0/5</td>
<td>0/2</td>
<td>0/1</td>
</tr>
<tr>
<td>Carcinoma of colon</td>
<td>13</td>
<td>0/9</td>
<td>0/4</td>
<td>0/7</td>
<td>0/3</td>
</tr>
<tr>
<td>Carcinoma of kidney</td>
<td>12</td>
<td>0/8</td>
<td>0/4</td>
<td>0/5</td>
<td>0/2</td>
</tr>
<tr>
<td>Carcinoma of stomach</td>
<td>11</td>
<td>0/4</td>
<td>0/7</td>
<td>0/4</td>
<td>0/4</td>
</tr>
<tr>
<td>Carcinoma of bladder</td>
<td>10</td>
<td>3/5</td>
<td>0/5</td>
<td>1/2</td>
<td>0/1</td>
</tr>
<tr>
<td>Carcinoma of prostate</td>
<td>10</td>
<td>1/9</td>
<td>0/1</td>
<td>1/5</td>
<td>0/2</td>
</tr>
<tr>
<td>Total</td>
<td>203</td>
<td>14/119</td>
<td>4/84</td>
<td>4/68</td>
<td>2/41</td>
</tr>
</tbody>
</table>

greater in the group scheduled to receive 50 µg/kg/week than in that scheduled for 75 µg/kg/week. An additional 36 patients were treated whose diseases were less frequently represented: carcinoma of the liver, 6; carcinoma of the testis, 5; carcinoma of the pancreas, 4; carcinoma of the uterus, 3; trophoblastic neoplasia, 2; mycosis fungoides, 2; neuroblastoma, 1; and miscellaneous neoplasms, 4. Of these, single instances of response were observed in good-risk patients with carcinoma of the pancreas, mycosis fungoides, and neuroblastoma and in 1 poor-risk patient with cancer of the rectum.

Response to vincristine, when recognized, occurred as early as 4 days and as late as 63 days after initiation of treatment with median onset times of 3 to 4 weeks. The responses were short with medians ranging from 2 to 11 weeks. No pattern of consistent difference in onset of remission or duration could be ascribed to the different dose levels or risk categories.

The influence of response on survival was measured. In Hodgkin’s disease, in both the good- and poor-risk categories, responders as a group survived longer than nonresponders despite risk category (Chart 1). In patients with lymphosarcoma, the survival of good- and poor-risk responders was about the same as that of nonresponders (medians, 3 to 7 months) until the last third of patients was reached, when the remaining responders, independent of risk, survived about 4 years, but nonresponders lived only approximately 1 year. In patients with reticulum cell sarcoma, the risk category appeared to dominate (median survivals of poor-risk patients, 0.5 and 1 month; those of good-risk patients, 2 and 4 months), with response imparting survival advantage. In patients with melanoma, the 3 responders in both risk categories demonstrated survival times (7 to 14 months) superior to the nonresponders (medians, 1 and 4 months). Similarly, among 187 patients with miscellaneous tumor types from Table 2, excluding melanoma, plus 36 patients from the text, responders in the good-risk category enjoyed greater survival than nonresponders (Chart 2).

Among patients with breast cancer, responders in both risk categories survive longer than nonresponsive patients treated with the same array of vincristine doses. Among
the nonresponders, good-risk patients survive longer than
poor-risk patients but not as long as poor-risk patients who
sustained response (Chart 3). The different survival time
of all responders (median, 12 months) from nonresponders
(median, 3 months) is not all due to the duration of rec-
ognizable remission. By subtracting the response days for
each patient from the survival time, one can construct a
hypothetical curve which still showed longer survival
(median, 10 months) for responding breast cancer patients
than for the nonresponders. It is possible that the drug has
effects on survival that are not correlated with clinically de-
tected tumor regression. Prognosis was estimated by the
clinical investigator at the time that patients entered on the
study. In patients with breast cancer, the prognosis for
47 nonresponding patients (23 good risk, 24 poor risk) was
rather accurately predicted, indicating some competence
in this clinical assay. Although estimates of prognosis for
the patients who eventually responded was somewhat longer
(11 of 15 of those patients came from the good-risk group),
the survival of the responding patients is considerably in
excess of the prognostication (Chart 4).

Factors in patients with breast cancer known to influ-
ence other forms of treatment were studied to assess their
effect on vincristine response. The youngest patient, age 31,
and the next to oldest patient, age 78, each enjoyed par-
tial remission. The remaining response were spread with-
out significant relationship to age. A variety of prior ther-
apies had been used for these women. Prior androgen or
estrogen administration and oophorectomy had no ap-
parent effect on frequency of partial remissions from vin-
cristine (10/37, 6/17, and 6/18 responses, respectively).
The prior history of antimetabolite or alkylating agent
- treatment, which usually followed endocrinological treat-
ments was associated with slightly lower response rate
(4/21 and 2/18 responses, respectively).

Thirty patients who had previously been treated with
vinblastine are arbitrarily classified as “poor risk” because
of it. The validity of this classification, adopted because
of potential cross-resistance or cumulative toxicity, was
demonstrated. Only 2 of 10 patients with Hodgkin’s dis-

Chart 3. Survival of patients with carcinoma of breast as influenced by
response to vincristine and by risk category. Responders: O, good risk, 11;

Chart 4. Predicted and observed survival times in 15 responding and
47 nonresponding patients with carcinoma of the breast. Responders: O,
survival time; •, predicted survival. Nonresponders: □, survival time;
■, predicted survival.

ease sustained partial remission, both at the 12.5-µg/kg
dose. One had previously failed on vinblastine and the
other had responded. The toxicity experience of these 10
patients was not different from that of the entire group of
Hodgkin’s disease patients. According to hematological,
biochemical, and prognostic criteria, 5 of the 10 patients
would have otherwise qualified for “good-risk” status.
One of these 5 sustained a partial remission, compared to
14 responders of the 22 patients similarly classified as
“good risk” who had not received vinblastine. Thus, al-
though cross-resistance is not absolute, there is probably
some decrease in responsiveness to vincristine after vin-
blastine treatment.

The duration of all responses to vincristine was influ-
enced by the risk status of the patients. Good-risk patients
enjoyed longer responses than poor-risk patients (Chart 5).
In 59 good-risk responding patients the durations of re-
missions occurring in patients randomized to doses of 25
and 12.5 µg/kg/week were longer than those at 50 or 75
µg/kg/week. Fourteen of 20 patients at the 2 low doses
took 10 or more injections, whereas only 15 of 39 at the

Chart 5. Remission duration as a function of risk status. O, good risk,
59; □, poor risk, 20.
higher doses did so, implying greater tolerance to the lower dose and a more sustained chemotherapeutic effect on the tumor with longer treatment.

Eighty-four patients treated up to 12 weeks (median, 2 weeks) had no toxicity ascribed to the drug (Table 3). Two of 22 patients with “responsive” tumor types sustained remission without toxicity. Thus it was possible to reach remission status without recognizable drug effect on normal tissues, but this was rare. The short median duration for treatment without toxicity reflects abbreviation of scheduled dose for reasons other than toxicity. Eighty% of these patients had died within 1 month, irrespective of initial prognostication.

With increase in toxicity to Grade 1, a higher percentage of responses was seen in the “sensitive” tumors. Response rates further increased in each of the 4 “sensitive” tumors with Grade 2 toxicity. Occasional patients with “sensitive” tumors who were treated to severe toxicity (Grade 3) showed lower response rates than those with Grade 2 toxicity. Miscellaneous tumor types show a broad plateau of antitumor activity of low order in the presence of toxicity, but no regressions occurred after treatments that were nontoxic. There was no difference in median remission durations among patients at different levels of toxicity. Highest response rates occurred with Grade 2 toxicity in both good- and poor-risk patients. More poor-risk patients (54/164; 33%) were classified as having no toxicity than were good-risk patients (30/229; 13%). This is probably ascribable to the difficulty in properly identifying mild toxicity in poor-risk patients and, to a lesser extent, to a lower mean dose for poor-risk patients, as the result of earlier deaths or removal from study because of moribund status.

Toxicity varied from acute and self-limited to delayed and irreversible and was most frequently of sensory, motor, or autonomc neurological type. Paresthesias, described as numbness, tingling, burning, or prickling, appeared in 284 patients (57%) and thus can be considered quite characteristic of vincristine administration (Table 4). The first appeared after 1 to 12 doses, but usually were present by the 3rd dose. The proportion of patients with paresthesias was nearly identical at the 4 dose levels. The median time to onset was shorter in the 75-μg/kg group, however, than at lower doses. Anesthesia was reported 16 times in 284 patients at the 2 higher dose levels but only once in 108 patients in the 2 lower dose groups. Paresthesias appeared in some patients after cessation of the drug. When the drug was stopped at onset of paresthesia, this symptom disappeared, albeit requiring many months in some patients. Paresthesias did not disappear while administration of the drug continued.

Deep boring bone pain in one or another part of the axial or appendicular skeleton occurred in one-fourth of the patients and constituted a recognizable clinical syndrome. It appeared as early as after the 1st injection or as late as the 15th week. Although the pain was often severe, the syndrome usually occurred only once, was self-limited, and disappeared over a period of days despite repeated injections of vincristine. A unique subtype of this deep pain was maxillary, mandibular, or throat pain. Excruciating pain in 1 of these regions might appear hours after the 1st or 2nd dose of vincristine. Pain appeared to be dose related, occurring but once in 108 individuals treated at the 2 low-dose levels, but in 23 instances of the 284 patients at the 2 high-dose levels.

Insomnia, anxiety, dreaming, torpor, and confusion were reported in a small number of patients. Since these phenomena occur with an indeterminate frequency in patients with cancer, their causality is not proved. More significant evidence of brain dysfunction occurred in some of the same patients and appeared dose related. Hallucinations were recognized 6 times, 5 of which were in the 75-μg group. Coma occurred 3 times, all in the 2 high-dose groups.

Areflexia of the patellar and Achilles tendons was nearly universal. Motor neuropathy was manifest as weakness of grip with clumsy functions involving the intrinsic muscles of the hand. Quadriceps weakness was also prominent. Ninety instances of muscle weakness were reported, all but 14 in the 2 highest dose levels. Wrist drop was reported 8 times, and foot drop or slapping gait 21 times. Most of the sensory and motor neuropathy eventually disappeared clinically, perhaps in part by compensatory neurological function. Atrophy of the interosseous muscles of the hands was sometimes first appreciated after drug administration had stopped. Clinical laryngeal paralysis occurred 5 times at the 2 higher dose levels. Immobility of 1 cord or weakness of both was demonstrated in the patients examined. Three patients were remarked to have blurred vision, without recognition of extraocular motor palsy or other.

### Table 3

Vincristine toxicity as a determinant of response (composite toxicity score)

<table>
<thead>
<tr>
<th>Tumor types</th>
<th>Carcinoma of breast</th>
<th>Hodgkin’s disease</th>
<th>Lymphosarcoma</th>
<th>Reticulosarcoma</th>
<th>Miscellaneous neoplasms</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>R/T*</td>
<td></td>
<td>R/T</td>
<td>R/T</td>
<td>R/T</td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>1/11</td>
<td>0/2</td>
<td>1/6</td>
<td>0/3</td>
<td>0/62</td>
<td>2/84</td>
</tr>
<tr>
<td>1</td>
<td>4/29</td>
<td>8/19</td>
<td>5/9</td>
<td>4/11</td>
<td>10/85</td>
<td>31/153</td>
</tr>
<tr>
<td>2</td>
<td>8/14</td>
<td>10/16</td>
<td>5/7</td>
<td>5/8</td>
<td>7/59</td>
<td>35/104</td>
</tr>
<tr>
<td>3</td>
<td>2/5</td>
<td>2/3</td>
<td>1/2</td>
<td>1/2</td>
<td>5/10</td>
<td>10/41</td>
</tr>
<tr>
<td>4</td>
<td>0/3</td>
<td>0/1</td>
<td>0/1</td>
<td>1/2</td>
<td>1/10</td>
<td>1/10</td>
</tr>
<tr>
<td>Total</td>
<td>15/62</td>
<td>20/41</td>
<td>13/26</td>
<td>9/24</td>
<td>22/239</td>
<td>79/392</td>
</tr>
</tbody>
</table>

* R/T, response/total treated.
insofar as the group of 4 tumor types which manifested the greatest percentage responses, when considered as a whole, showed no decrease in tumor response with decreasing dose. This may have been attributable to fewer injections of the prescribed high doses because of interruptions for toxicity.

Stratification of patients by risk category was accomplished in advance by estimation of survival for greater or less than 2 months. The classification of 164 patients of 392 as having a prognosis of less than 2 months is evidence that the patient population was indeed a sick one. The data cast some light on drug response in patients with far-advanced cancer. Response rates were higher among good-risk patients than among poor-risk patients (Tables 1 and 2). The duration of responses was short in most patients even if called "complete" at the beginning; in poor-risk patients the duration was even shorter (Chart 5).

The accuracy of clinical estimates of survival was demonstrated in the survival curves of nonresponding patients classified as good or poor risk. The survival of 107 nonresponding good-risk patients with miscellaneous cancers was longer than 87 poor-risk patients (Chart 2). In smaller groups of patients with breast cancer (Chart 3), reticulum cell sarcoma, and melanoma, and possibly in patients with Hodgkin's disease (Chart 1) and lymphosarcoma, the survival times of nonresponders with good-risk status (prognosis estimated >2 months) were longer than poor-risk (prognosis estimated <2 months) nonresponders. These observations indicate that physician can estimate survival in patients with advanced cancer with some accuracy. In all disease entities, good-risk or poor-risk patients who sustained response survived longer than patients in the same risk category who did not respond. The argument might be advanced that drug response merely selected patients with inherent biological advantage who were destined to survive longer. This supposition, however, would appear to be an unlikely explanation for the survival time of some responding patients who were originally classified as poor risk. In patients with breast cancer, melanoma, and Hodgkin's disease, survival of the 11 poor-risk patients who sustained response was longer than for good-risk patients who did not respond. The effects of treatment thus exerted greater influence than the biological characteristics which led to a classification of poor risk, and it is reasonable to accept a causal role of the vincristine therapeutic response in prolongation of survival.

The relationship of estimated prognosis and drug response to survival were analyzed in greater detail in patients with breast cancer. The longer survival time of responders is not simply an increase due to the time in remission. The possibility exists that duration of therapeutic effectiveness on the factors that determine survival is different from the obvious regression time of tumors. Additional support for a role of vincristine in survival extension of responding patients with breast cancer is seen in Chart 4. Estimated prognosis for 47 nonresponding patients is a reasonable approximation of the observed survival. The actual survival of the responding patients, however, is considerably in excess of their prognosis. These

**DISCUSSION**

Appreciation of a somewhat different spectrum of tumor activity for vinblastine and vincristine in rodent tumors (6) and in preliminary human trials (1, 4) led to the present multiclinic study. The study was initiated at a dose known to elicit antineoplastic effects in pilot studies. When activity was again seen, successive decreases in dose were comparatively studied. This extrapolation was successful reported abnormality.

Drug effects on the alimentary tract were prominent. Troublesome constipation was reported in one-third of all patients, with greater frequency, severity, and earlier onset in the highest dose group. Three patients who received 75 µg/kg sustained adynamic ileus requiring medical decompression. Eight additional patients with intra-abdominal neoplasms suffered intestinal obstruction, usually recognizable as adynamic ileus from which 4 died.

Abdominal pain was a common accompaniment of other bowel symptoms ascribed to vincristine. The pain frequently occurred after the 1st or 2nd injection and preceded the discomfort associated with established constipation. Such pain was dose related: 23% in those who received 75 µg/kg, but only 10% at the 3 lowest doses.

Impotence appearing during treatment was reported frequently by 1 investigator. It may be presumed that other observers were not as assiduous in their questioning.

Effects on rapidly growing normal tissues were sought. No mucosal ulceration attributed to the drug reported. Leukopenia <5,000/cu mm appeared in 41 to 57% of all patients independent of dose. Depression of white blood cells count to <2,000/cu mm was seen in 7 to 10%, equally distributed among dose levels. Thrombocytopenia (<100,000, 8 to 11%; <50,000, 4 to 10%) was also independent of dose. Concomitant abnormality in both these hematological parameters was uncommon. Anemia was not prominent or clinically distinguishable from that of patients chronically ill with cancer. Megaloblastosis or macrocytosis was not reported. Drug effects on hair growth were prominent. Alopecia of scalp hair was reported in 13 to 22%, although other body hair was unaffected. Alopecia was never permanent, and regrown hair was sometimes more pigmented and curly than previously. Extravasation of the drug caused cellulitis, vesiculation, and slough.

### Table 4

Neurological toxicity from vincristine (other sensory phenomena)

<table>
<thead>
<tr>
<th>% of patients at dose levels of</th>
<th>75 µg/kg (170 patients)</th>
<th>50 µg/kg (114 patients)</th>
<th>25 and 12.5 µg/kg (108 patients)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Paresthesias</td>
<td>58</td>
<td>56</td>
<td>56</td>
</tr>
<tr>
<td>Mild</td>
<td>32</td>
<td>33</td>
<td>38</td>
</tr>
<tr>
<td>Moderate</td>
<td>18</td>
<td>18</td>
<td>15</td>
</tr>
<tr>
<td>Anesthesia</td>
<td>6</td>
<td>4</td>
<td>1</td>
</tr>
<tr>
<td>Deep pain</td>
<td>27</td>
<td>21</td>
<td>14</td>
</tr>
<tr>
<td>Maxillary, mandibular, or throat pain</td>
<td>7</td>
<td>10</td>
<td>1</td>
</tr>
</tbody>
</table>
data are subject to 2 interpretations. One is that the present investigators were reasonably able to prognosticate short survivals but were unduly pessimistic about patients who would live a median of about 1 year. The other interpretation is that the demonstrated capability to prognosticate in nonresponders was systematically rendered invalid because of an effect of vincristine on more prolonged survival than on recognizable inhibition of tumor growth.

Hormonal treatments or endocrine ablation for breast cancer did not adversely effect response rate to vincristine. Prior vinblastine treatment of several neoplasms did not evoke uniform cross-resistance to vincristine. No appreciable difference in tumor regression was found at different scheduled dose levels, perhaps because of premature decrease or discontinuation of toxic high-dose levels. There was, however, a striking correlation of drug effects on normal tissues (toxicity) and tumor response (Table 3). The sensory, motor, and autonomic toxicity classified as Grade 2 operationally as rarely accepted as “moderate” by patients. At that toxicity grade, however, the tumor response rate among the 4 “sensitive” tumors ranged from 57 to 71%. The fact that these same 4 neoplasms had lower response rates when toxicity was absent or Grade 1 (mild) is evidence that effects on tumor tissue and normal tissue increase in nearly parallel fashion. In this series of patients with this drug, the question “Is toxicity really necessary?” (2) must be answered in the affirmative up to Grade 2 toxicity. Further clinical experience may redefine the extent of clinical toxicity to which a patient should be exposed to achieve tumor regression, and increase in survival. The failure of patients with Grade 3 or 4 toxicity to demonstrate increased tumor regression may be related to such severe dysfunction of the host that tumor regression did not occur prior to death or forced interruption of drug therapy.

The similarity of the response experience by toxicity grade in both good- and poor-risk patients reinforces the conclusion that tumor response occurred with greater frequency as a biologically more significant dose was administered. There would appear to be an unambiguous reason for rejecting vincristine treatment to a severely toxic endpoint. Since the patient may become incapacitated from neurotoxicity at high doses while tumor responses do not improve and may even decrease, our data suggest that a dose level between 25 and 50 μg/kg, administered until signs of mild neurotoxicity, should elicit tumor response if it is going to occur. Other workers have indeed found that 35 μg/kg is a suitable dose in breast cancer (7) and 25 μg/kg is suitable in lymphosarcoma (3).

The biochemical explanation for the unique neurotoxicity of vincristine is not precisely known (9), and the mechanism of its effect on the spectrum of human cancers have reported is not established (5, 8). Insight into these 2 areas might allow enhancement of the clinical usefulness of vincristine. Considerable improvement has already been found using vincristine in combination for some neoplastic diseases. These opportunities have not been exhausted.

REFERENCES

Vincristine Treatment of Advanced Cancer: A Cooperative Study of 392 Cases

James F. Holland, Carol Scharlau, Salman Gailani, et al.

*Cancer Res* 1973;33:1258-1264.

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