Concurrent Combination Chemotherapy of Human Solid Tumors: Experience with a Three-Drug Regimen and Review of the Literature

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SUMMARY

Our own experience together with that reported in the literature with the use of nonhormonal concurrent combination chemotherapy of human solid tumors is reviewed. Sixty-eight patients, with tumors known to be relatively drug resistant received a combination of antitumor agents including mitomycin C, melphalan, and vincristine. Fourteen objective responses were seen in fifty-three adequately treated patients. Median duration of response was 9 weeks, with two responses exceeding six months. Toxicity was generally moderate, with the most severe manifestation as bone marrow suppression. Six of eighteen adequately treated patients with sarcoma and two of four patients with parotid cell carcinoma exhibited responses. A variety of approaches which may enhance the effectiveness of combination chemotherapy in solid tumors are discussed.

INTRODUCTION

Theoretical interest in the possibilities of the use of multiple drug therapy to increase the therapeutic index of antitumor agents dates to the 1950's with the work of Goldin (9), Potter (32), Elion (5), Skipper (39), and Lepage and Sartorelli (24, 34, 35). At about this time a number of investigators also attempted clinical evaluation of drug regimens involving two or more chemotherapeutic agents (26, 27). A resurgence of interest in combination chemotherapy in human solid tumors resulted from reports of improved results with multiple drug regimens in lymphoma and leukemia, as reported by Freireich et al. (7) in childhood leukemia, by Thompson et al. (41), Frei (6, 8), and Karon (19) in adult leukemia and by DeVita (3, 4), and Lacher (22) in Hodgkin's disease. The question now arises, a decade after the first clinical use of concurrent combination chemotherapy in solid tumors, whether combination chemotherapy has improved results in tumor types less sensitive to single drug chemotherapy. In an attempt to answer this question, fifteen studies of nonhormonal combination chemotherapy of human solid tumors have been reviewed. In addition, we have studied 68 patients treated with a three-drug regimen and will analyze our experience in this group.

MATERIALS AND METHODS

"Therapy B" (31) consisted of mitomycin C (4) 0.1 mg/kg/week, plus phenylalanine mustard (melphalan) 0.2 mg/kg/week, plus vincristine (Oncovin) 0.025 mg/kg/week. This group of agents was chosen because it included an alkylating agent (phenylalanine mustard), a plant alkaloid (vincristine), and an antibiotic (mitomycin C). While all of these agents are bone marrow depressants, the toxicity of vincristine is primarily neuropathic. Melphalan induces gastrointestinal toxicity, whereas neither mitomycin C nor vincristine exhibit this type of toxicity as a dose-limiting side effect. The first forty patients treated with this regimen were randomized with an alternate three-drug regimen ("Therapy A") including 5-fluorouracil, actinomycin D, and cyclophosphamide. Because significantly more responses were seen in "Therapy B," twenty-eight additional cases were studied on this protocol. The age of patients ranged from five to eighty-seven years (mean forty-five years). Thirty-seven patients were male and thirty-two were female. Forty-five patients had been treated with other drugs, X-irradiation, or both prior to the use of "Therapy B." They were chosen because they had tumors of types known to be resistant to other drugs or had failed to respond to them (Table 1). All diagnoses were established by biopsy. A summary of the tumor-type, number of patients who received an "adequate" course of therapy (defined as more than three weeks on treatment), and the objective tumor responses observed (defined as greater than fifty percent decrease of all measurable lesions for longer than two weeks) are reviewed in Table 1.

Patients were seen at least once a week, and all measurable lesions were noted on standard flowsheets of the Eastern Cooperative Oncology Group. Routine weekly studies included measurement of the patient's weight, hemogram, and serum chemistries, including lactic dehydrogenase, alkaline phosphatase, blood urea nitrogen, uric acid, and bilirubin. At appropri...
ate intervals, routine urinalysis, stool guaiac, serum calcium, and serum phosphorus were also determined. When neoplastic disease was demonstrable by chest X-ray and/or metastatic series, or liver scan, these films were obtained every three to eight weeks.

Drug doses were modified because of toxicity in the following fashion: the dose was reduced to half when the white blood count was between three thousand and five thousand per cubic millimeter, the platelet count was between seventy-five thousand and one hundred thousand per cubic millimeter, and/or when moderate nausea and vomiting or progressive paresthesias developed. When the white blood count was below three thousand per cubic millimeter, the platelet count below seventy-five thousand per cubic millimeter, or when severe nausea and vomiting or severe progressive paresthesias were noted, the drug was omitted. If neuropathy was the sole dose-limiting toxicity, vincristine alone was terminated, while the other two drugs were continued. Alopecia occurred in eight patients and was slowest to appear (7.0 weeks). Signs and symptoms of toxicity were not significantly greater in patients who responded than in those who did not. Two patients expired during periods of drug-induced marrow suppression.

Therapeutic results in sixty-eight patients are summarized in Table 1. Seven of fourteen responses occurred in patients with carcinomas of a variety of histologic types, representing a response rate of twenty percent of adequately treated patients. Of special interest were the responses in two of four patients with parotid adenocarcinomas, a tumor usually relatively resistant to chemotherapy. Six of eighteen adequately treated patients with a variety of sarcomas had responses, yielding a thirty-three percent response rate for these usually extremely refractory tumors. One of nine adequately treated patients with malignant melanoma had an objective response.

DISCUSSION

Studies of combinations of chemotherapeutic agents have attempted to utilize drugs exhibiting differing modalities of toxicity, each of which is tolerable, while achieving additive or positive synergistic antitumor effects (31, 36). These antitumor effects may result from biochemical blockade of either multiple synthetic pathways (5) or of multiple sites in a single synthetic pathway (32) of protein or nucleic acid metabolism.

The degree to which these hypotheses have achieved practical implementation is demonstrated in Table 3, which summarizes data obtained from fifteen previous clinical studies of nonhormonal concurrent combination chemotherapy of solid tumors. A number of these studies have been concerned with specific tumor types such as breast cancer, lung cancer, neuroblastoma, or carcinoma of the testis. The extensive experience with choriocarcinoma has not been included because it is mostly concerned with sequential rather than concurrent com-
They included alkylating agents, antimetabolites, natural products, antibiotics, and synthetic steroidal drugs. The dose schedules have varied but generally involved the simultaneous administration of one-half to one-third of the usual single drug dose of two to four agents. Toxicity was generally regarded as comparable to single drug therapy. One author (30), however, felt that toxicity was significantly more severe than with single drug treatment. All studies except one (30) reported some objective responses, and six studies (10, 11, 13, 17, 18, 26) stated that they had achieved a response rate in excess of that seen with single drug therapy alone. However, in only three studies (11, 13, 33) was randomization between multiple and single drug therapies carried out in a prospective fashion. In one study (28) comparison was made with other multiple-drug regimens. The quality of responses achieved was variable. In certain tumors generally regarded as “drug sensitive,” such as neuroblastoma (18) and choriocarcinoma of the testis (26), the duration of response was measured in months to a year. In other studies dealing mainly with patients with “drug insensitive” tumors or patients who had received extensive prior chemotherapeutic treatment, response was generally poor and was measured in weeks to less than three months (12, 28). Two studies specifically commented on the failure to achieve greater response rates than might have been anticipated with the use of single agents (23, 33). Evidence of prolongation of survival was observed in one study of patients with lung cancer (16), but this was not considered better than that achieved by X-ray alone in another study of the same disease (27).

Comparison of these results with our experience in the study of sixty-eight patients treated with a combination of mitomycin C, melphelan, and vincristine emphasizes a number of points. A review of prior therapy in our patients shows only one objective response among twenty-three patients who had a history of previous treatment with chemotherapeutic agents (Table 1). On the other hand, thirteen of forty-six patients with no prior history of chemotherapy had objective responses. Thus, it is apparent from the onset, that patients who have been extensively treated or who are in poor clinical condition will tend to exhibit poorer response to subsequent therapy. Whether specific drug cross-resistance was a factor here is not clear. Talley’s studies suggest that cross-resistance between two different classes of drugs (5-fluorouracil and Cytoxan) is possible (40). No consistent relations were seen in our study.

The types of tumor treated (Table 1) were quite variable but, generally speaking, were relatively “drug insensitive.” It is of some interest that six of eighteen adequately treated patients with sarcoma had objective responses, a response rate probably superior to that previously reported for single agents (Table 3). Seven of twenty-six adequately treated patients with carcinoma responded, a number of which might have been expected in single drug therapy. However, this group included few “drug sensitive” tumors such as carcinomas of the colon or breast. In the case of parotid carcinomas, two of four patients responded, which suggests a specific activity of this patient or combination therapy in this histologic type of carcinoma. It should be noted that, because no responders were seen in patients who had inadequate therapy, response rates indicated in Table 1 would be higher if they were calculated including only adequately treated patients. This observation again confirms the probability that patients in generally poor clinical condition, who are less likely to tolerate a full course of treatment, are significantly less likely to be good responders. The median duration of response of nine weeks (mean 14 weeks) (Table 1) is relatively short. However, exceptional responses lasting over twenty-eight and sixty-one weeks were observed in two patients.

Toxicity with this combination of agents was moderately severe (Table 2). About 60 percent of the patients experienced either mild to moderate bone marrow suppression, gastrointestinal upset, or both, and almost half the patients exhibited neuropathy, presumably due to vincristine. Gastrointestinal upset tended to be most rapid in onset but was less common and milder than leukopenia. Bone marrow suppression appeared next, followed by neuropathy and alopecia as the toxicities appearing latest. In two patients, death associated with leukopenia and infection may have been related to drug toxicity.

There is a suggestion, from our experience and that reported in the literature, that tumors which tend to be relatively “drug insensitive” may be those which are more responsive to combination chemotherapy than to single agents. Whether this is due to their greater sensitivity to drugs with different mechanisms of action is not clear. Talley’s studies suggest that cross-resistance between two different classes of drugs (5-fluorouracil and Cytoxan) is possible (40). No consistent relations were seen in our study.
<table>
<thead>
<tr>
<th>Author</th>
<th>Date</th>
<th>Drug</th>
<th>Disease</th>
<th>Toxicity</th>
<th>Total No. of patients</th>
<th>No. of patients evaluable</th>
<th>No. of objective responses</th>
<th>Tumor types</th>
<th>Comments</th>
</tr>
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<tbody>
<tr>
<td>W. Luhrs</td>
<td>1957</td>
<td>Triethylene melamine</td>
<td>Bronchogenic carcinoma</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Survival as good as that with X-ray therapy.</td>
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<td></td>
<td></td>
<td>6-Mercaptopurine Methotrexate</td>
<td></td>
<td></td>
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<tr>
<td>J. D. Hurley et al.</td>
<td>1960</td>
<td>Methotrexate</td>
<td>Multiple tumors</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Proved better than single agent. Suggestive increase in survival randomized with single agents.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Triethylene melamine 6-Mercaptopurine</td>
<td></td>
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</tr>
<tr>
<td>M. C. Li et al.</td>
<td>1960, 1967</td>
<td>Methotrexate Actinomycin D Chlorambucil</td>
<td>Carcinoma of testis</td>
<td>Mostly mild and reversible</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>7 complete responses; mean duration 6 months. More effective than single agents.</td>
</tr>
<tr>
<td>L. A. Leone et al.</td>
<td>1961</td>
<td>Mechlorethamine</td>
<td>Multiple tumors</td>
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<tr>
<td></td>
<td></td>
<td>Actinomycin D</td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td>No increased response rate over single agents. Prolonged i.v. infusion used.</td>
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<tr>
<td></td>
<td></td>
<td>Triethylene thiophosphoramid + actinomycin D</td>
<td></td>
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<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Triethylene thiophosphoramid + actinomycin P₂</td>
<td></td>
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</tr>
<tr>
<td>D. E. Kayhoe</td>
<td>1964</td>
<td>Methotrexate Vincristine 5-Fluouracil Cyclophosphamide</td>
<td>Multiple tumors</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>E. M. Greenspan</td>
<td>1965</td>
<td>Triethylene thiophosphoramid Methotrexate Cyclophosphamide 5-Fluouracil Testosterone</td>
<td>Breast carcinoma</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>9/9 responses with hepatic metastases</td>
</tr>
<tr>
<td>J. Horton et al.</td>
<td>1965</td>
<td>5-Fluouracil Mitomycin C Vincristine Triethylene thiophosphoramid</td>
<td>Miscellaneous</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Lung Melanoma Breast</td>
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<tr>
<td>D. H. James</td>
<td>1965</td>
<td>Cyclophosphamide Vincristine</td>
<td>Neuroblastoma</td>
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</table>
Table 3 (Continued)

<table>
<thead>
<tr>
<th>Author</th>
<th>Date</th>
<th>Drug</th>
<th>Disease</th>
<th>Toxicity</th>
<th>Total No. of patients</th>
<th>No. evaluable</th>
<th>No. of objective responses</th>
<th>Tumor types</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>L. Nathanson et al.</td>
<td>1966</td>
<td>Mitomycin Vincristine Phenylalanine mustard 5-fluorouracil Cyclophosphamide Actinomycin D 5-Fluorouracil 6-Mercaptopurine Methotrexate</td>
<td>Multiple tumors</td>
<td>0 deaths</td>
<td>2</td>
<td>40</td>
<td>28</td>
<td>2 deaths</td>
<td>4/11 sarcoma 2/4 parotid</td>
</tr>
<tr>
<td>J. Horton et al.</td>
<td>1967</td>
<td>5-Fluorouracil Mitomycin C Triethylene thiophosphoramide Fluorescein</td>
<td>Multiple adult tumors</td>
<td>&gt;5-fluorouracil alone</td>
<td>56</td>
<td>10</td>
<td>4/22 colon 3/12 breast 2/6 unknown primary 1/2 rhabdomyosarcoma</td>
<td></td>
<td></td>
</tr>
<tr>
<td>R. J. Reitemeier et al.</td>
<td>1967</td>
<td>Fluorometholene 5-Fluorouracil</td>
<td>Gastrointestinal carcinoma</td>
<td>3 deaths</td>
<td>32</td>
<td>32</td>
<td>4</td>
<td>2/10 stomach</td>
<td>Randomized with each agent alone.</td>
</tr>
</tbody>
</table>

Nonhormonal concurrent combination chemotherapy of human solid tumors.
sensitive," such as leukemia and neuroblastoma, may well have a marked augmentation of rate and/or quality of response with combination chemotherapy. However, in tumors which tend to be relatively drug insensitive, combinations of agents, each of which produces a relatively low rate of response or poor quality of response, did not seem to improve the speed or completeness of response. It should be emphasized, however, that with relatively low degrees of antitumor effect true synergism may be demonstrable only with extremely large groups of patients.

A number of possible approaches might be used to remedy this situation. First, relatively little attention has been paid to drugs whose primary action may be to actually ameliorate toxicity of other agents rather than to promote increased antitumor effect. The role of drugs such as prednisone, testosterone (1), progesterone, nonandrogenic anabolic agents, and phytohemagglutinin (15) or specific antagonists of toxicity, such as citrovorum factor with methotrexate (25), in allowing an increase over usually tolerable drug doses of an active antitumor agent should be reviewed. Another possibility in certain solid tumors would be that of identifying more specific biochemical parameters to deal with. Use, for example, of agents which inhibit the pathways of melanin synthesis in malignant melanoma has only recently been explored (2), as has the possibility of the use of antagonists to serotonin in malignant melanoma (14, 37). Whether other similar specialized pathways can be discovered in sarcomas or bronchogenic carcinomas, for instance, remains to be seen. The use of combinations of agents by special routes, such as intraarterial infusion or perfusion, also is an area which remains to be explored (21). It is hoped that by such methods as these theoretical advantages of combination chemotherapy in solid tumors may be finally realized.

REFERENCES

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