Combined Radiotherapy and Chemotherapy of Lymphomas and Other Cancers

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Summary

Although studies of combinations of radiation therapy and chemotherapy have shown some indication of usefulness, there is little evidence at present supporting their routine utilization for any type of localized cancer.

However, the long-term control in a portion of patients with Hodgkin’s disease from multiple chemotherapeutic agent programs suggests eradication of tumors in these patients, indicating a possible alternative to the extension of radiation therapy to clinically uninvolved areas in the early stage of Hodgkin’s disease in future therapeutic trials.

This report includes data from a study of combination vincristine versus placebo during radiation therapy for lymphoma. Significantly better tumor response was seen at the end of radiation therapy, with suggestive improvement in relapse and survival rates in those given the vincristine.

Data regarding the tolerance of patients previously treated with extensive radiotherapy during intensive multiple agent chemotherapy indicated little evidence of greater hematological toxicity or decreased percentage of scheduled drug actually delivered as compared to a group of patients not previously irradiated. Response rates to the chemotherapy program were nearly as high in the previously irradiated group as in those not previously irradiated.

Introduction

Several years ago, when Burchenal (2) reviewed the utilization of drugs and radiation for various forms of human cancer, he posed the question as to whether these 2 kinds of therapeutic modalities were competitors or partners. At that time he felt that there was little competition, since radiotherapy could be curative for certain types of localized disease, whereas chemotherapy is almost never curative in any type of cancer.

A corollary of this position would note that radiotherapy can be of little value in the cure of disseminated cancer with visceral involvement.

However, recent developments in therapy of Hodgkin’s disease have seen considerable change in both of these therapeutic principles. Data upon the intensive multiple agent chemotherapeutic approach have revealed a sizable proportion of long-term, disease-free survivors and would seem to indicate the probability of cure in some of these patients (6, 29, 35).

The ability of radiotherapy applied to extended ports both above and below the diaphragm to produce long-term effects in Stage III patients with Hodgkin’s disease is now well accepted (18), and the principle of such total nodal therapy is now being applied to patients with Stage I and II disease. Furthermore, techniques of visceral radiation, such as the inclusion of the entire liver into fields to which is delivered a dosage high enough to eradicate disease within the port, are being utilized (19).

The improvement in the techniques of both radiotherapy and chemotherapy as they pertain to Hodgkin’s disease would indicate that an area of competition in curative attempts in some categories has developed. It is also apparent that Hodgkin’s disease patients’ tolerance to therapy has been seriously underrated in the past and that the application of combinations including both radiotherapy and chemotherapy given electively to patients during their most responsive period of first therapy is entirely appropriate. It is the purpose of this report to review the background of such combinations and to present some new data from related studies.

Mechanism of Action of Combination Chemotherapy and Radiotherapy

There would appear to be 3 ways by which combinations can operate (Table 1).

Potentiation versus Antagonism

Although there has been considerable discussion as to whether additive or synergistic activity for various combinations of therapeutic agents has been seen in vitro or in vivo, any type of potentiation from agents which act somewhat differently one from the other may be of clinical interest. In laboratory models, examples ranging from intense antagonism to mild potentiation have been observed (40). When agents are evaluated in animal experiments with transplantable tumors, the contribution of transplantation immunity can complicate interpretation of data (26, 27).

In a clinical setting, data regarding potentiation or antagonism are of little importance unless a favorable change in the therapeutic index can be obtained, allowing better destruction of tumor as compared to normal tissues. In this regard, the experimental animal work of Bruce et al. (1), in which colony-forming cells from both lymphoma and normal hematopoietic tissue are used, may be of much value. Such studies allow time-dosage relationship studies of the effects of various drugs and radiation therapy upon the vital stem cell populations of the 2 kinds of tissues, with demonstration of possible advantages in therapeutic index. Their work indicates
that radiotherapy and nitrogen mustard kills at all positions of the generation cycle. Drugs such as vinblastine, vincristine, and cytosine arabinoside kill cells at only 1 portion of the generation cycle but demonstrate excellent therapeutic index in favor of tumor kill up to a saturation dosage. Cyclophosphamide, 5-fluorouracil, and actinomycin D showed no saturation dosage, with a much better tumor cell kill than hematopoietic stem-cell kill.

Despite these experimental data, there has been little clinical evidence of examples of interference between drugs and radiation. However, Johnson and Brace (16) suggested the possibility that previous chemotherapy had altered radiation response of Hodgkin's disease, based upon the observation of a 38% incidence of relapse in such patients within radiation port, whereas a small control group of patients without chemotherapy prior to radiation had no recurrence.

Synchronization

Despite the data cited above, there is considerable evidence of a general pattern of radiosensitivity related to the cell cycle (24). Most cell lines are most sensitive in mitosis, with a resistant peak in G1, followed by gain in sensitivity in late G1 or early S phase. Another resistant peak occurs late in S or in early G2. Late in G2, cells may be almost as sensitive as cells in mitosis. In rapidly growing neoplasms, such as lymphomas, the comparatively long-duration S phase may result in a relatively large portion of cells occupying this phase.

Since several agents may act directly (e.g., methotrexate or 5-fluorouracil) or indirectly (e.g., cytosine arabinoside or hydroxyurea) as DNA-blocking agents resulting in mitotic arrest, a higher proportion of cells may be brought into cell-cycle synchrony which would allow an increased radiotherapy effect.

A possible example of clinically useful synchronization in children with acute leukemia by utilization of 2 drugs has been reported by Lampkin et al. (21, 22), who administered a single dose of cytosine arabinoside followed in 72 hr by a single dose of vincristine. Repeated bone marrow aspirates showed a rapid decrease of mitotic figures and uptake of tritiated thymidine, then recovery to pretreatment levels or above in 72 hr. At this time vincristine was given, resulting in a high rate of DNA synthesis and a much higher peak of mitotic figures 72 hr after vincristine than was usual after the drug, which suggested recruitment of resting cells by the careful timing of the 2 agents.

While such synchronization may be possible, present data do not allow the formulation of models of dosage and timing of diverse agents upon different normal and tumor tissues at a clinical level at this time.

Experience With Nonlymphomatous Cancer

There is a large background of clinical data concerning the utilization of chemotherapeutic agents as adjuvant therapy to the radiation of solid tumors, which are often resistant to radiation. Although a number of agents devoid of antitumor activity themselves have shown some activity in experimental situations, none except hyperbaric oxygen has reached any degree of clinical utilization.

Hydroxyurea has preferential cytotoxic effect in the S phase of hamster cells, the passage of cells from G1 to the S period being blocked until removal of the drug, following which the surviving cells were more sensitive to X-ray (34). Others, working with spleen colony formation, showed an additive effect of hydroxyurea and X-irradiation, irrespective of whether irradiation was given prior or after drug therapy (41).

Hydroxyurea is undergoing clinical trials as a radiosensitizer. In a recent report, the drug was compared to a placebo in head and neck tumors, in which considerable evidence of potentiation of effect by the drug, particularly in regard to cervical lymph node metastasis, was noted (32).

Cyclophosphamide started immediately after diagnosis and followed by radiotherapy has shown some promise in small pilot studies in Ewing's sarcoma; the patients remained free of disease for longer than expected periods (13, 15).

5-Fluorouracil has been used in a number of trials in combination with radiotherapy. Negative (10) or equivocal (38) results were seen with bronchogenic carcinoma. Some evidence of an additive effect has been seen with 5-fluorouracil and radiation upon tumors of the head and neck, especially when given intraarterially (14, 20, 38). Further trials of a prospective nature for this type of tumor are in progress. Negative results were obtained in carcinoma of the breast, bladder, laryngopharynx, uterine cervix, and glioblastoma multiforme (38). In a small group of patients with various carcinomas of the gastrointestinal tract, it was not possible to increase the result from adequate radiation, but some usefulness may have been present when the full dose of radiation could not be given (12).

Methotrexate given alone has considerable activity in carcinoma of the head and neck and may be a worthwhile adjuvant to radiotherapy of these relatively radioresistant tumors. Initial studies have indicated a 68% complete response (20) and a 2-year survival rate of 35% in another (8). The mucositis reaction to treatment with the combination was greater than from radiation alone (26).

Actinomycin D has a firm investigational background as a radiation potentiator. It has been variously claimed to produce a G1 and G2 arrest as well as a partial block in mitosis. It produces an increased skin reaction when used during radiotherapy, and other normal tissues (e.g., intestinal
epithelium) probably have increased sensitivity to damage (3). This drug is used routinely in the early intensive therapy of Wilm's tumor and, along with surgery and radiation, an overall survival rate of 80% has been achieved (4). In another series, the survival rate from surgery and irradiation of 34% was increased to 61% by the addition of actinomycin D (23). However, no randomized study of prospective nature is available, and the increased survival in Stage III may be the only group in which the drug makes a useful contribution (25). The drug had no value combined with radiation for lung cancer (10). This drug and triethylenemelamine has been used with radiation therapy for retinoblastoma in an attempt to keep the necessary dosage of radiation at a lower range (36).

With the use of an experimental group of alkylating agents known as “dual antagonists,” some degree of potentiation of radiation effect upon bronchogenic carcinoma at the low dosage of 1800 rad was observed; this was thought to be comparable to results in those treated with radiation alone to doses of between 3000 and 5000 rad (37). However, pulmonary reactions to the therapy were also of equal severity, suggesting potentiation of damage of the normal tissue.

Procarbazine, although ineffective alone, was used with radiation therapy for 26 patients with mesothelioma, with response in 54% while 9 patients treated with radiation alone failed to respond (7).

**Application of Combined Radiotherapy and Chemotherapy to Lymphomas**

In view of the generally satisfactory response of lymphomatous tumors to radiation therapy alone, there has been little interest in the routine utilization of combinations of drugs and radiation to potentiate tumor shrinkage. However, resistant tumors do make up some proportion of cases, particularly in the reticulum-cell sarcoma or Hodgkin's sarcoma group, in which techniques of combination therapy might be applied to advantage.

There are a number of situations, some of which were recently reviewed by Gamble et al. (9), in which the combination of drugs and X-ray may be of value in lymphoma therapy (Table 2).

Although the fear of radiation edema from intensive radiotherapy has led to the utilization of drugs for relieving pressure from obstructive syndromes, Rubin et al. (33) have recently reported good results of spinal cord compression from high-increment irradiation alone.

**Vincristine and Radiation Therapy**

In a recently completed study at Roswell Park Memorial Institute, 50 patients were randomized to receive 3 weekly doses of either vincristine or placebo in a double-blind fashion during a course of radiation therapy for malignant lymphoma. The patients had late-stage disease and large tumors or were considered to have disease at least partially resistant to former therapy. There was no restriction of the radiation dosage, which averaged about 3000 rad (depth dose) (Table 3). There were 3 patients with giant follicular lymphoma, 7 patients with lymphosarcoma, 14 patients with Hodgkin's disease, and 25 patients with reticulum-cell sarcoma. Vincristine dosage was either 2 or 3 mg as the 1st weekly dose and 2 mg on the succeeding 2 doses given during the 2nd and 3rd week of radiation.

The tumor response within the radiation port at the end of the therapy, was significantly better \( p < 0.025 \) in the vincristine-treated group (Table 4), with 55% complete response as compared with a 19% complete response in the placebo control group.

The final maximal response of the irradiated tumor was also better in those receiving vincristine (Table 5); complete

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**Table 2**

**Indications for combination chemotherapy and radiotherapy for lymphoma**

1. Potentiation of radiation effect for better tumor shrinkage in certain resistant tumors or for those recurring within a former therapy port.
2. To allow lower radiation dosage during therapy of tumors in organs easily damaged by X-rays, e.g., lungs or kidneys.
3. During initial therapy to Stage IV patients with a dominant tumor mass in one area which can be treated locally followed by chemotherapy for the smaller disseminated foci.
4. Before radiotherapy to shrink huge tumor masses to allow more reasonable X-ray port size, e.g., mediastinal tumors.
5. As “medical decompression” on an emergency basis for obstructive syndromes of veins cava, spinal cord, or airways prior to radiation.
6. To control systemic symptoms, e.g., fever, prior to radiation.

**Table 3**

**Radiation dosage**

<table>
<thead>
<tr>
<th>Depth dose (rad)</th>
<th>Vincristine group</th>
<th>Placebo group</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;1000</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>1000–2000</td>
<td>4</td>
<td>2</td>
</tr>
<tr>
<td>2000–3000</td>
<td>13</td>
<td>6</td>
</tr>
<tr>
<td>3000–4000</td>
<td>11</td>
<td>10</td>
</tr>
<tr>
<td>&gt;4000</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Total</td>
<td>29</td>
<td>21</td>
</tr>
</tbody>
</table>

**Table 4**

**Response of study tumor at end of therapy**

A significantly better tumor response at the completion of radiation therapy was seen in the group receiving vincristine as compared to the control group.

<table>
<thead>
<tr>
<th>Type of response</th>
<th>Vincristine-radiotherapy</th>
<th>Placebo-radiotherapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients</td>
<td>%</td>
<td>No. of patients</td>
</tr>
<tr>
<td>None</td>
<td>1</td>
<td>4</td>
</tr>
<tr>
<td>Partial</td>
<td>12</td>
<td>41</td>
</tr>
<tr>
<td>Complete</td>
<td>16</td>
<td>55</td>
</tr>
<tr>
<td>Total</td>
<td>29</td>
<td>100</td>
</tr>
</tbody>
</table>

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**Combined Radiotherapy and Chemotherapy**

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responses were observed in 79% of this group, as compared to 57% complete response in those given placebo with radiation, but this was not significantly different.

Relapse of the irradiated tumor was observed in only 17% of the vincristine-treated patients and in 26% of the control group, despite evidence of progressive disease elsewhere in many of the patients.

Survival of those receiving the chemotherapy has been better than that of the controls (Table 6). The 50% survival time for the vincristine-radiotherapy group was 13 months, as compared to 5 months in those receiving radiotherapy alone. Eleven of the chemotherapy group are living, while only 3 of the control group survive.

Although inadvertently there were more patients with giant follicular lymphoma and lymphosarcoma in the group receiving vincristine, better results were seen in all the diagnostic categories when vincristine was given, and 6 of the 11 survivors in the drug-treated group had Hodgkin’s disease.

Thus, a better local tumor response to the irradiated area was seen by the addition of vincristine during radiation. Since the relapse rate was not high in either group, the better survival seen in those treated with vincristine during radiation is probably due to the drug effect on the disease outside the radiation area.

**Combination Therapy to Achieve Cure of Lymphoma**

In the experimental animal with transplanted lymphoma, marked potentiation of radiation can be achieved by nitrogen mustard, cyclophosphamide, vincristine, and vinblastine (30). The potentiation upon cure rate is also seen at full doses of regional radiotherapy, apparently due to control of metastatic disease.

A prospective randomized British study compared the survival of 97 patients with Stage I and II Hodgkin’s disease, one-half of whom were given a single dose of nitrogen mustard, 0.3 mg/kg, as soon as possible following at least 2500 rad to affected and adjacent node areas (11). Survival data have shown a significant difference at the 3-year point, with a 70% rate survival of the group treated with radiation alone as compared to an 88% rate in those receiving the combined therapy (31).

Somewhat more vigorous chemotherapy was utilized by Moxley et al. (28) in a trial of 3 cycles of multiple-agent therapy including cyclophosphamide, vincristine, methotrexate, and prednisone administered to 14 patients with Stage I or II disease. Radiation was delivered to involved areas only. A complete remission rate of 86%, with prolonged duration of remission, was obtained. The authors expressed a preference for chemotherapy first, to be followed by radiation.

These studies indicate a definite field of usefulness of combination radiation and chemotherapy for future therapy and suggest an attractive alternative or supplement to total nodal therapy, especially in the patients with difficult staging situations in which widespread disease is suspected either on anatomical grounds or by the presence of toxicity. The results of studies now underway will be of considerable importance. The utilization of multiple agents given over a long period would seem as important as sufficient dosage of radiotherapy in the design of future studies.

**Tolerance and Toxicity to Intensive Combinations**

A fear that patients would be unable to tolerate needed chemotherapy upon relapse after extended radiotherapy has proven for the most part groundless. Johnson et al. (16) have reported recovery from most hematological toxicity within 2 to 4 months following completion of extended-field radiotherapy. The marrow granulocytic reserve returns to normal 5 months after the completion of such therapy (39). However, Curran and Johnson (4) reported poor tolerance of 50% of the heavily irradiated group for approximately 12 months after therapy.

The tolerance of patients formerly treated with radiotherapy, during a period of intensive 6-month courses of either 4- or 5-drug combination therapy given either in combination or sequentially, was analyzed during the course of an Acute Leukemia Group B study of therapy of Hodgkin’s disease activated in 1967.

Of 246 patients, 83 had not received prior radiation therapy. A group of 105 had received radiation to 1 to 3 major lymph node areas; this group would have included those treated with a mantle-type port to all lymph node-bearing areas above the diaphragm or its equivalent. A 3rd group of 58 patients had received more widespread therapy, usually including areas on both sides of the diaphragm.

Hematological toxicity was rated from + to ++++ severity for each course (Table 7). There was little or no evidence of increased toxicity in those most heavily irradiated in the past.
Table 7

Hematological toxicity during multiple agent chemotherapy according to amount of prior radiotherapy

The degree of hematological toxicity of patients treated with intensive 4- or 5-drug multiple-agent routines over a 6-month period revealed no correlation with the number of radiation therapy courses delivered during the earlier stages of disease.

<table>
<thead>
<tr>
<th>No. of radiotherapy areas</th>
<th>Maximal degree of toxicity (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0</td>
</tr>
<tr>
<td>None</td>
<td>83</td>
</tr>
<tr>
<td>1–3</td>
<td>105</td>
</tr>
<tr>
<td>&gt;3</td>
<td>58</td>
</tr>
</tbody>
</table>

The only suggestion of such a relationship was in the +++ group, and this trend is not supported by increased ++++ toxicity of this group.

Furthermore, the formerly irradiated group was able to receive adequate dosage of the drug. Those without former radiation were given 81% of the scheduled drug therapy, while those with 1 to 3 areas of radiation tolerated 80% of the compounds, and those more heavily irradiated were given 76%.

A history of former radiation did not seriously interfere with the response rates obtained with the multiple-drug therapy. An overall response rate of 83% in those previously given radiation is less than the 95% obtained in those without prior therapy, but the rates of complete responses were nearly identical at 56%.

References

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