Chemotherapeutic Implications of Staging in Hodgkin’s Disease

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Summary

The chemotherapeutic implications of staging are the following. (a) As both radiotherapeutic and chemotherapeutic treatment programs become more aggressive, the decision as to what stage a patient resides in becomes more important since both programs may be mutually exclusive. (b) More complete approaches to staging are yielding previously unappreciated areas of disease involvement. More and more patients are exhibiting less and less localized disease. The implication may be that Hodgkin’s disease, particularly in reference to splenic involvement and vascular invasion, may metastasize more often than previously appreciated. (c) Development and application of chemotherapy for Hodgkin’s disease has now reached the point where it provides the therapy of choice for patients with Stage IIIB and IV disease and may be even more useful in patients with minimal amounts of widespread disease of the type uncovered by current staging techniques. (d) With our better understanding of the natural history of Hodgkin’s disease and the availability of two alternative therapeutic approaches, we should now be able to approach intelligently the design and execution of clinical trials within given stages of disease. (e) The question as to whether removal of the spleen is useful in allowing delivery of more chemotherapeutic agents with less toxicity in the newly staged patient is unsettled and will require such a controlled clinical trial for the answer.

Introduction

The current staging classification of Hodgkin’s disease was designed primarily to take into consideration the limitations of radiotherapy. Since X-irradiation, particularly with the older equipment available in the 1950’s, could not be delivered in effective doses to certain critical organs or to extensive areas of the body, it was necessary to delineate the extent of the lymph node disease and exclude those patients with organ involvement. It is not surprising then that, as radiotherapy has improved technically, the staging classification should be enlarged to make more cases eligible for radiotherapy.

Coincident with the development of the more aggressive radiotherapeutic approaches to Hodgkin’s disease has been the refinements of the approach to staging which has culminated in the staging laparotomy (10, 11). One of the most important pieces of information to be derived from the staging laparotomy has been that more and more patients have less and less localized disease, particularly with regard to previously unsuspected disease in the spleen. Although splenic involvement has been thought to represent direct extension from paraaortic nodes, many more patients have splenic involvement without paraaortic node disease demonstrable than the reverse. This fact and the patterns of disease in the spleen suggest that splenic involvement represents metastatic spread rather than local extension. Further support for this point of view comes from recent work from Dr. Rappaport’s group in Chicago (20, 23). They have demonstrated vascular invasion by Hodgkin’s disease, particularly in those with the more advanced histological types. They have also began to correlate vascular invasion with risk of recurrence, particularly in sites not contiguous to the original biopsy. Splenic involvement by metastatic spread may account for the failure of the most radiotherapy programs to cure about one-third of these patients with apparently localized disease. No one has yet correlated vascular invasion directly with splenic involvement, but such data would be extremely important.

What does all this have to do with chemotherapy? The point is that, even before the advent of the staging laparotomy, about 35% of patients at our institution presented with Stage IV disease. If splenic involvement or the presence of demonstrable vascular invasion in the original biopsy should prove to indicate the presence of metastatic disease, or at least in the case of splenic involvement a high risk of tumor in the liver, then there will be an increasing need for some effective form of systemic therapy. An effective systemic therapy would very likely be used earlier, particularly as an adjuvant to current radiotherapeutic approaches. All the experimental evidence available supports this approach since it points to the fact that chemotherapeutic agents are more effective in patients with a smaller volume of disease.

The remainder of this review will be concerned with the background and development of the alternative approach to the treatment of Hodgkin’s disease, chemotherapy, and will provide some updated information on a recently published combination drug program developed at the National Cancer Institute (7).

Experimental Evidence for Intensive Drug Treatment

Before we review the results of the chemotherapy of Hodgkin’s disease, it is important to review the background of experimental evidence that led up to the more intensive treatment programs in use today and the reasons for considering Hodgkin’s disease a candidate tumor for aggressive treatment.

Physicians treating patients with advanced cancer have been faced with 2 major frustrations: (a) administering an antitumor agent and watching the tumor grow; and (b) giving other patients with equally advanced cancer an antitumor agent and watching masses of tumor completely disappear,
only to regrow in a relatively short period of time. The first type of tumor is thought of as resistant to drugs, and those in the latter category are considered drug-responsive tumors. The latter experience is by far the more frustrating of the two for all concerned, because it holds out the most promise for success and is the least understood.

For some understanding of the clinical phenomena surrounding responses to treatment and recurrences in responsive tumors, investigators in the early 1960’s turned to the drug-sensitive animal tumor, the transplantable murine leukemia, L1210. Studies by Skipper et al. (21) with this tumor model have provided the basis for what is now known as the cell kill hypothesis. This hypothesis states that prolongation of survival following therapy in animal tumors, and presumably those in man, is quantitatively related to the number of cells killed by treatment. These investigators reconfirmed an older observation by Furth and Kahn (9) that a single injected leukemic cell was capable of growing and killing the host. In Skipper’s studies, the larger the number of cells injected, the shorter was the survival. Survival could be predicted from a knowledge of the number of injected cells, the generation time of individual tumor cells, and the volume-doubling time of the tumor. If the increase in survival following cytotoxic agents is largely due to the cytocidal effects of treatment, then by extrapolating back from the duration of survival after treatment, an estimate of the fraction of the cell population killed can be made with considerable accuracy. By using the prolongation of survival as an indication of numbers of tumor cells killed, this group showed that a dose-response relationship existed between numbers of cells killed and dose of an effective drug.

In the mouse bearing leukemia L1210, a particular drug treatment eliminated a constant fraction of the tumor cell mass, not a constant number of tumor cells per dose. This latter principle, although sometimes difficult to understand, is referred to as the logarithmic order of death and has been well known to bacteriologists dealing with germs for years (3, 22). It is extremely important, since it implies that, given a sensitive tumor system, the favorable circumstances for successful therapy exist when the cancer cell population is small or when the dose of the effective drug can be increased without harming the normal host cells. In addition, in leukemia L1210, combinations of drugs have been used to increase survival or cure the host under circumstances when single drugs are relatively ineffective (27). The medical oncologist rarely finds himself faced with small cancer cell populations, since the average 1-ml mass probably contains as many as $10^9$ cells. When effective drugs are available, these principles can best be exploited in adjuvant chemotherapy programs when patients appear to be free of tumor following surgery or radiation, 2 regional forms of treatment, but are known to have a high risk of recurrence because of nonregional spread. Patients who have evidence of Hodgkin’s disease in the spleen with or without microscopic proof of liver involvement might be considered in such a category.

It is apparent to everyone that L1210 leukemia in the CDF1 mouse is quite different than most cancers in man. In leukemia L1210, the volume-doubling time of the tumor is equal to the generation time of the average cell (28). This indicates that, within the time-span of one cell replication, all the cells in the tumor population will begin to progress through the cell cycle. This characteristic seems to be commonly present in transplanted tumors, particularly after several transplant generations, but not in spontaneously arising tumors of man or even mice. This rapid proliferation largely accounts for the high curability. Such rapidly growing populations can be expected to be more susceptible to therapy than even the most rapidly growing normal tissue, the bone marrow stem cell pool. The latter seems to be true because some bone marrow stem cells appear to remain in a resting, nonproliferative state until called upon to replace depleted reserves; at this time, their sensitivity to an otherwise acceptable dose of drug is sharply increased (1, 26). This latter phenomenon has highlighted the importance of the scheduling of drug doses in maximizing antitumor effect and minimizing toxicity. The short treatment periods often required for effective treatment of rapidly proliferating leukemia L1210 cells very likely avoid exposing mouse bone marrow to repetitive insults at the least opportune times. As a further complication of the transfer of mouse data to man, the kinetics of mouse bone marrow appears to be markedly different than that of human marrow (4). Generation, storage, and exit times of mouse cells are about one-half the duration required in man. Cell cycle data in human tumors are limited, but the available data suggest that the major difference between animal tumors and human tumors is not the generation time of their individual cells but the number of cells in cycle at any one time (29). That is, in human tumors the growth fraction appears considerably less than unity. Although resting, the “out of cycle” cells have the potential for growing and causing the death of the host if repeated and prolonged chemotherapy is not given. All of the tumor cells in such a population are unlikely to be killed by a single exposure to drugs.

Criteria for Drug Combination Treatment Programs

The systematic exploration of combinations of drugs in man followed the development of the above principles in mice. The apparent differences between mouse and man do not negate the principles derived from the treatment of the sensitive animal tumors but should serve to point out that the treatment of human tumors will require different drugs, different doses, and different schedules, based on avoiding limiting bone marrow toxicity but still exposing the tumor cells to longer durations of repetitive treatment. If one considers the reports of successful clinical drug combination programs, certain criteria appear to be necessary before one can expect success from any combination drug treatment program in man (12). (a) The tumor in question must be one of the drug-responsive tumors; (b) each drug to be used in combination should have independent activity against the disease (that is, it should not be cross-resistant to the other available drugs); (c) when there is a choice of several chemicals within a class of agents, the selection of the agent to be used in combination should be based on avoidance of overlapping side effects with other agents in question (such a selection may lead to the use of each drug in full or nearly full doses); (d) since resistance to any of the agents in question leads to
Vincent T. DeVita, Jr., and Paul P. Carbone

reduced therapeutic efficacy without diminishing toxicity, it is preferable that previously untreated patients be entered into such studies.

There are several types of tumors that are considered drug sensitive in man: the acute leukemias, trophoblastic tumors, tumors of the testes and ovaries, Wilm's tumor, carcinoma of the breast, and the lymphomas, particularly the Burkitt's lymphoma and Hodgkin's disease. There is considerable evidence that the use of intensive drug regimens, often in combination, has improved the survival of the patients bearing these tumors (12).

Data Derived from the Use of Single Agents in the Treatment of Hodgkin's Disease

In 1963, 20 years of chemotherapy experience had led to the development of 4 classes of antitumor agents, each with significant and independent antitumor effects against the Hodgkin's tumor: the alkylating agents; the Vinca alkaloids; the methylhydrazine derivative, procarbazine; and the corticosteroids. Table 1 summarizes data collated by Nixon and Ultmann (25) from most of the available literature. A response was defined as a 50% reduction in tumor mass lasting longer than 2 months. The usefulness of such a response is minimal to the patient, but it does serve to indicate that the drug in question has a potential for beneficial effect against the disease. The results with the Vinca alkaloid, vincristine, are not shown in Table 1. Vinblastine is generally considered the drug of choice in this class of chemicals, but what data are available suggest that there is no difference in the response rate between the 2 drugs in comparable patients. There are several points of interest. First of all, although the overall response rate is high, the percentage of patients who have complete disappearance of their tumor, clearly the most beneficial of responses, is small. In most studies, the complete response rate for any of the above drugs rarely exceeds 20% (2). The average duration of response to single agents is short, approximately 6 weeks, and appears related to the magnitude of the reduction of tumor mass, since the average duration of a complete remission, after cessation of treatment, is twice as long as that of a partial response. Maintenance of the remission with continued drug administration can prolong the response to as long as 8 months for patients having good initial responses to the drugs. In a controlled study already referred to above, it was also clear that prior treatment compromised the chance of obtaining complete responses to subsequent drug (2).

Whether single drug treatment has improved survival of patients with advanced disease is a favorite topic for discussion. Those physicians who care for many patients with Hodgkin's disease feel that there are clear examples in their clinics of prolongation of useful life (24). Since prolongation of life appears related to the magnitude of the response to the drug, as long as the complete response rate remained as low as 20%, the median survival was not likely to reflect the benefit achieved in those few responding patients. The median survival, in the past, for patients with Stages III and IV of Hodgkin's disease, measured from the institution of drug treatment, has almost invariably been less than 24 months (2, 19). Interestingly enough, in the previously mentioned controlled clinical trial (14), survival of patients with Hodgkin's disease was not influenced by whether the response was maintained with continued drug treatment or the patient was allowed to relapse before retreatment.

The Results of Combination Chemotherapy

In 1963, the use of the available effective drugs in combination in the treatment of Hodgkin's disease began to be explored (5, 8, 14). The early results showed a higher complete response rate. Our approach was to use short, intensive bursts of chemotherapy, with rest intervals between each treatment, to allow for recovery of the host, hopefully without leaving enough time for regrowth of the tumor. Our primary goal was to increase the percentage of complete responses. As a guide to the magnitude of tumor cell kill, we planned to use the duration of the response from the last day of therapy. No drug maintenance was planned. We felt that the available data indicated that the absence of drug maintenance treatment would not compromise the patient's survival. Ultimately, survival of the patients would reflect the overall benefit of the program. After a pilot study was conducted to test the feasibility of using these drugs safely in combination (17), the program was modified slightly and begun in its present form in 1964 (6). Since that time, over 125 patients with advanced Hodgkin's disease have been treated with the

<table>
<thead>
<tr>
<th>Drug</th>
<th>No. of patients</th>
<th>No. improved</th>
<th>Mean duration of remission with no maintenance (mo.)</th>
<th>Mean duration of remission with maintenance therapy (mo.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nitrogen mustard (no maintenance)</td>
<td>215</td>
<td>131 (61%)</td>
<td>2.5</td>
<td></td>
</tr>
<tr>
<td>Nitrogen mustard and maintenance on chlorambucil</td>
<td>38</td>
<td>260 (59%)</td>
<td>3.0</td>
<td>7.0</td>
</tr>
<tr>
<td>Cyclophosphamide</td>
<td>441</td>
<td>353 (64%)</td>
<td>2.0</td>
<td>6.5</td>
</tr>
<tr>
<td>Vinblastine</td>
<td>551</td>
<td>430 (75%)</td>
<td>4.0</td>
<td></td>
</tr>
</tbody>
</table>

Table 1 Response of patients with Hodgkin's disease to various drugs

Improvement was defined as greater than 50% reduction of tumor masses lasting longer than 2 months. Number improved include complete and partial responses.
combination drug program. Between 1964 and July 1967, 43 previously untreated patients with advanced disease entered the study (6). This group has a minimal follow-up of almost 4 years and, since the responding patients have been handled differently since July 1967, it is most appropriate first to examine the drug program and the results in this group of 43 patients.

The treatment program is shown in Table 2. A brief comment is in order about the drug scheduling and the duration of the treatment program. As indicated previously, we had an idea that these aspects would be important, but we had little data on which to base our design. The actual proliferative capacity of this tumor was not known, but it was expected to be characterized by a growth fraction less than unity. We therefore thought that repeated therapy would be required. The treatment was spread over a 2-week period, rather than giving it as a single bolus or over a 24-hr period, the schedules which are most effective in rapidly growing mouse tumors. The proper duration of time to treat these people is still not known, but 3 months of treatment in the pilot study, although effective, proved too short; longer than 6 months seemed impractical because of the expected progressive marrow suppression. Therapy was therefore administered in a cyclical fashion for 6 months. Each cycle is given over a 2-week period and was followed by a 2-week rest interval before institution of the next cycle. A sliding scale was used to reduce the doses of the drugs if the patient’s bone marrow had not entirely recovered from the last treatment.

Each drug indicated in Table 2 was given in full therapeutic doses. Prednisone was administered only during the 1st and 4th cycle. The doses in Table 2 are in mg/sq m of body surface area. Vincristine was selected as the Vinca alkaloid to avoid overlapping bone marrow suppression. Cyclophosphamide, in equivalent doses, was used instead of nitrogen mustard in 12 patients to avoid thrombocytopenia, but the latter side effect did not seem to be a great problem in either case. However, the added alopecia was a problem, so we returned to our original use of nitrogen mustard. When analyzed separately, the group treated with cyclophosphamide was not significantly different with regard to acute and chronic toxicity or response, so the results are considered together. Details of the administration of these drugs, the toxicity associated with them, and staging and characteristics of the patients in question are available for review (7).

Table 2
A single cycle of the combination drug program

<table>
<thead>
<tr>
<th>Drugs</th>
<th>Day 1</th>
<th>Day 8</th>
<th>Day 14</th>
<th>Day 28</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vincristine</td>
<td>1.4</td>
<td>1.4</td>
<td>Rest period</td>
<td></td>
</tr>
<tr>
<td>Nitrogen mustard</td>
<td>6</td>
<td>6</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Procarbazine</td>
<td>100</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prednisonea</td>
<td>40</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*a Cycles 1 and 4 only.

While discussing toxicity, one additional aspect of the staging laparotomy must be considered in regard to chemotherapy, and that is the effect of splenectomy. Will removal of the spleen allow the administration of more drugs with less toxicity? There have been no studies designed to answer this question in a controlled way. When we examined the amount of drugs which patients were able to receive in our standard group compared to a small number who had had surgery with splenectomy primarily because of equivocal lymphangiograms, those with spleens, if anything, received more drugs. These are selected data and the differences are not significant. It has always been reversible in patients who have achieved complete remission.

Toxicity, although occasionally severe, was tolerable. Suffice it to say that almost all the patients received their treatment as outpatients. Although we feel that this type of therapy can be given safely in a Hematology-Oncology Clinic geared for such studies, its toxicity would probably not be acceptable for occasional use by physicians. Nausea and vomiting were temporary and controllable. Alopecia was not a major problem after we stopped using cyclophosphamide. The dose-limiting toxicity was, as expected, bone marrow suppression; the most annoying side effect to the patient was the neurotoxicity produced by vincristine. The latter effect has always been reversible, and the former was controllable with the sliding dose reduction scale. About 20% of the patients did develop rather severe bone marrow depression, requiring marked reductions in doses. Most of the patients were quite ill at the time therapy was instituted, and 2 factors made the program acceptable to them. First, the rapid improvement in their clinical condition, with the disappearance of symptoms and evidence of tumor, often surpassed the discomfort from drug side effects. Second, therapy was projected for a finite period of 6 months rather than indefinitely. In fact, the overall time commitment to treatment for these patients was not significantly different, in our opinion, than the use of the same drugs singly. We have had only 2 drug-related deaths, both from rapid necrosis of tumor, bowel perforation in one patient, and necrosis of a pulmonary mass, lung abscess, and sepsis in another. Organ toxicity has invariably been reversible in patients who have achieved complete remission.

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had more than one organ involved with tumor. Table 4 gives details of the response to treatment. These data have been updated to March 1971. Of the 43 patients treated, 35 (81%) had complete disappearance of their tumor. A complete response was defined as the disappearance of all evidence of tumor and a return to normal performance status. Six patients, although they responded with marked reduction in the size of their tumor, failed to achieve a complete remission and were designated remission induction failures. On the average, it took about 3 months to obtain a complete remission.

With a minimum follow-up time of almost 4 years, 20 of the 35 complete responders have relapsed, but 15 patients remain free of disease for periods up to 6 years from the end of treatment. The median duration of the response is 36 months from the end of all treatment. This is far in excess of the average duration of complete remissions after single drugs. The median time to relapse in those 20 patients with recurrent disease was 11 months. The most interesting aspect of this study, I believe, is that, of those patients at risk for 4 years, 48% remained continuously free of their disease with no further treatment. At 5 years, this figure is 41% (Table 5). An added and unexpected dividend has been that those patients who relapse following a good remission are easily retreated with the combination. Once these patients are successfully retreated, they are intermittently reexposed to the drug combination rather than leaving them entirely without therapy again. When one examines all the patients at risk for 4 years, 81% remain alive. The difference between the 47% continuously free of disease and the 81% figure represents those patients with recurrent disease who have been successfully retreated. As shown in Table 5, for those patients in the entire group at risk for 5 years, 72% are alive. Seventy-seven % of the complete responders at risk for that interval are surviving.

A life table analysis of the survival of these patients is shown in Chart 1 with the population divided into those over and under age 30. As with many illnesses, age at diagnosis influences survival; the younger patients have a better overall prognosis than those in the older age category. Since 27 of the patients remain alive, and most of these are presently free of their disease, either continuously from the end of treatment or as a result of retreatment, the median survival, now in excess of 4 years, should be considerably longer.

In addition to age, stage of disease played an important role in the prognosis. All the induction failures and all but one death were in the Stage IVB category. At our institution, the survival of patients with Stage IIIB disease treated with combination chemotherapy appears superior to those treated with total nodal irradiation alone. We have now begun to explore the use of both modalities of treatment in this group of patients.

When the results of treatment were related to the histological classification, we were somewhat surprised. The patients were about evenly divided among lymphocyte-depleted, mixed cellularity, and nodular sclerosing Hodgkin's disease, according to the Lukes and Butler classification (16). Although the numbers are small, the nodular sclerosing group has fewer patients free of disease and
more deaths than the other 2 categories. If this trend continues, the results will be the reverse of what is generally noted in radiotherapy studies.

The responding patients have not had their immunological status impaired; in fact it has improved. Seventy % of the patients skin tested before treatment were anergic. Of those anergic patients retested after treatment, 66% had recovered their ability to respond to delayed hypersensitivity antigens, an encouraging finding which is compatible with the general good health of these patients. These data illustrate an important point. Where effective treatment programs are available, the beneficial effect of eradicating tumor seems to override the potential hazard of the use of potent immunosuppressive agents. This fact has been well illustrated in animal models (13).

Confirmatory evidence for the effectiveness of drug combinations in Hodgkin’s disease has been published. Another study using the same drug program, with vinblastine substituted for vincristine, has been reported from Great Britain by Nicholson et al. (18). Complete responses were obtained in 86% of patients with advanced disease who had received no prior therapy. This group of patients is most comparable to those described above in our study. An additional group of patients in their study who had received radiotherapy in the past had a complete remission rate of 79% while those who had received chemotherapy with or without prior radiotherapy had a less impressive response rate (35%). Toxicity did not appear prohibitive. Although the substitution of vinblastine for vincristine appeared to alleviate the neurotoxicity observed with our program, the drug-induced leukopenia seemed more severe in the British study and required longer intervals for reversal than seen with National Cancer Institute study.

We have also studied a group of patients who had received extensive prior therapy to determine whether combinations of drugs would possibly be of benefit in such patients (15). Much to our surprise, to complete response rate, and thus far the remission duration, in those patients who had received prior therapy with only total nodal X-irradiation was comparable to those patients who had had no prior treatment. Patients with extensive prior chemotherapy, particularly with alkylating agents, or chemotherapy plus X-irradiation, fared the worst as in the British study. In the National Cancer Institute study, the doses of drugs had to be reduced and often the intervals between cycles were prolonged because these previously treated patients appeared to have compromised bone marrow function.

The follow-up period was too short in the British study to provide comparative data on remission durations and ultimate survivals for the good responders, but these kinds of data are clearly the most important. Currently, there are several studies in progress to compare combination drug programs to single drugs or other new combination programs, and to examine the effects of further treatment after achieving remission on the ultimate disease-free survival. If refinements in staging continue to identify more patients who are candidates for systemic therapy, the results of the types of studies mentioned above will assume even greater importance and are eagerly awaited.

As with every other disease and therapy, the results are better when the best treatment is used earlier. Our current complete response rate has fallen to 70% since we no longer include patients with Stage IIIA and IIIB in the program in which drugs alone are used, and patients with Stage IVA disease are uncommon. Patients with those 3 stages in the original group never failed to achieve a complete response, and the recurrence rate is lower than in patients with Stage IVB disease. I do not find this fact discouraging. While we look for better treatment programs for the patients with very advanced disease, we should be encouraged to use our best systemic therapies earlier but in a controlled way.

I believe it is not presumptuous to state that, when one deals with a sensitive tumor with effective agents, intensive treatment improves the response rate and improvement in survival follows. The principles derived in the animal models seem to apply. However, the current treatment programs are still too empiric. Hopefully, their design will be improved when we understand the biology of the human tumors to the same degree as the animal models. Certainly, we also need better tools to improve on the results.

References
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