Chemotherapy as a Primary Treatment of Hodgkin’s Disease¹

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Summary

Chemotherapy is not indicated as the primary treatment of Stage I and II Hodgkin’s disease. In Stage III Hodgkin’s disease, the results of therapy, as determined from published studies, are approximately the same with chemotherapy or radiation therapy as the prime form of therapy, and perhaps somewhat better when both are employed. For certain complications of Hodgkin’s disease chemotherapy is the initial treatment of choice. The present data do not allow us to conclude if alkylating agents or the more newly introduced chemotherapeutic agents have a useful adjunctive role in the treatment of Stage I or II disease; nor have the newer agents been as extensively evaluated as the alkylating agents for the optimal role that they play in the management of advanced Hodgkin’s disease.

Introduction

For many diseases there is general agreement with regard to the broad outlines of therapy and only technics vary. In the malignant lymphomas, and especially Hodgkin’s disease, there are several partially efficacious forms of therapy and there are large areas of their application in which there is no consensus. This discussion is directed to one of the more controversial areas, the use of chemotherapy.

Before discussing the therapeutic aspects of chemotherapy, it may be appropriate to make some comments regarding other ways in which chemotherapy might contribute to overcoming obstacles to the control of Hodgkin’s disease.

It is quite likely that the use of chemotherapeutic agents in the study of the fundamental aspects of cell biology will make significant contributions to our understanding of neoplasia. Evidence in this direction has been accumulating steadily (11). Saber and Balis have used 6-mercaptopurine to uncover variations in the enzymes of nucleotide interconversion in different tissues (10). Actinomycin D has proved to be a valuable tool in probing the function of messenger RNA (23). Frei et al. have studied the effects of vincristine on the mitotic activity of malignant lymphoma and carcinoma cells (8). The mitotic index thus obtained could conceivably be a useful parameter of biologic activity. The remarkable specificity of vinblastine for Hodgkin’s disease, a specificity which largely excludes related diseases of the same organ system, clearly carries with it important but as yet undeciphered information concerning the nature of Hodgkin’s disease. The very fact that Hodgkin’s disease responds to such a wide variety of therapeutic agents presents a further challenge in understanding this disease, which differs in so many ways from other neoplasms. The aforementioned, and other cyto genetic, biochemical, and morphologic studies, have been performed in individual lymphoma patients, but there has been no organized investigation to determine if any or all of them could be correlated with the clinical course or natural history of the disease.

One of the problems has been obtaining fresh material for these studies. For the most part, patients who arrive at a referral center for treatment of lymphomas already have their diagnosis established. The hospital at which the initial biopsy is performed is seldom equipped to do special studies, and the physicians at the referral center seldom feel justified in performing another biopsy. However, if the total facilities of the research institute were brought to bear on the individual patient and he were made to understand the potential rewards of such integrated clinical and preclinical research, it is likely that most patients would voluntarily submit to another biopsy. At the same time the continual flow of human material into the laboratories would increase the clinical participation of such facilities, and the ensuing dialogues between clinician and basic scientist would be stimulating to both.

The remaining portions of this presentation will deal with the therapeutic role of chemotherapy in Hodgkin’s disease. It should be mentioned at the onset that there is no question as to the primacy of radiation therapy in the treatment of Hodgkin’s disease. In certain situations radiation therapy is curative; no one has made such a claim for chemotherapy. Further, there is little question that chemotherapeutic agents provide useful palliation of symptoms of Hodgkin’s disease. The chief problem is to determine the optimal roles of these agents in a disease which may require their use under many different circumstances.

A. Chemotherapy in the Treatment of Early Hodgkin’s Disease

In the following 3 studies, alkylating agents combined with radiation therapy were used in the treatment of early Hodgkin’s disease and the results compared with the use of radiation therapy alone.

Paterson (15) treated 67 patients with Stage I Hodgkin’s disease with radiation therapy (32 patients) or nitrogen mustard plus radiation therapy (35 patients). There was no remarkable difference in the 5 year survival rates between the 2 groups (59 and 54%) or in the length of the 1st remission of the disease (50 and 46 months). Cook et al. (4) did a similar study with 212 patients and found virtually identical survival rates in both groups. However these cases were not randomized, and in general the patients receiving nitrogen mustard were in poorer condition. The authors conclude that the results of the 2 clinical groups

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employing Trenimon (a benzoquinone carrier of ethyleneimino since the poorer clinical group, in effect, caught up with regard notes that the results of Peters (16) with radiation therapy alone groups). His results were distinctly better in patients receiving alkylating agent and radiation therapy. However, the author notes that the results of Peters (16) with radiation therapy alone were very close to his best results—those obtained with his combination groups.

B. Chemotherapy in the Treatment of Late Hodgkin’s Disease

In a group of patients in which nitrogen mustard was the principal form of therapy, Hall and Olsen (10) found an 8% 5-year survival rate; this was comparable to the results of Peters (16) in the treatment of Stage III Hodgkin’s disease with radiation therapy alone (9%). Gelhorn and Collins (9) compared the treatment in 132 Hodgkin’s disease patients with irradiation alone, or nitrogen mustard followed by supplementary radiation therapy as needed. The 4-year survival rates of the patients in these 2 groups were approximately the same (52.3% and 54.8%). The authors point out that the length of survival from the time of dissemination of disease favored the combination therapy group (43.5 months versus 34.3 months) but that this difference was not statistically significant. However, there were some practical aspects of management brought out in this study. In the chemotherapy-treated group the patients’ symptoms were more rapidly controlled. In addition, over the entire course of the disease the amount of radiation therapy required in this group was half that of the group treated with radiation alone. The total cost of medical care was reduced, and the number of visits to the hospital was decreased. On the other hand, patients in the combination therapy group had 7% significant morbidity and there was 1 death attributed to nitrogen mustard. In this study there was 78% subjective and objective improvement after the nitrogen mustard. This response rate is virtually the same as that reported in the study of Dameshek et al. (79.4%) (5). In Hall and Olsen’s study a meaningful measurement of the duration of remissions was not considered feasible, but in the study of Dameshek et al. (5) and that of Alpert and Peterson (1) it has been noted that the duration of remissions after nitrogen mustard is usually shorter than with radiation therapy. There are many exceptions to this, however, and the clinical setting must be better defined for a valid interpretation of such observations. In the aforementioned study by Linke (13) patients with Stage III disease were also studied, and in this group as well as those with less extensive disease the survival rate of the combined therapy group exceeded that of patients treated with irradiation alone.

Roos and Videbaek (18) compared the survival rates in 172 patients treated between 1930 and 1945, with 117 patients treated between 1946 and 1955. During the latter period alkylating agents, adrenal corticosteroids, and antibiotics were employed in addition to radiation therapy. At 3, 5, and 7 years the survival rates favored the latter group. In a similar study by Peters and Middlemiss (17) the group receiving chemotherapy in addition to radiation therapy in the course of the disease had a better survival rate at 1, 2, and 5 years, with the difference in results being most marked at 1 year. However Shimkin et al. (21), who also compared the survival rates in different “eras of therapy” could not find any significant difference as a result of the introduction of medical therapies. The survival rate in 108 patients treated before 1940 was 29.1% at 5 years. Of 112 patients seen from 1940 to 1948 the survival rate was 27.7%. This type of study is not very satisfactory since one cannot be sure that the groups of patients in the 2 time periods were comparable. Further, since the 1st clinical reports on the use of nitrogen mustard did not appear until 1946, Shimkin’s study does not take us very far into the chemotherapy era. Since we are continually comparing alkylating agents with radiation therapy, it is well to keep in mind Shimkin’s figure of 23.3 % 5-year survival rate for untreated patients. The 5-year survival rate in this series for all patients treated with radiation therapy was 26.4%. It is generally agreed, survival rates notwithstanding, that in the symptomatic patient with generalized Hodgkin’s disease, alkylating agents have decreased the morbidity due to this disease.

In virtually all of the above studies the alkylating agents employed were nitrogen mustard or triethylenemelamine given in single or a few doses and not repeated until symptoms returned. There are 2 studies of interest in that the alkylating agents were given in a different fashion.

In the study of Larionov at the Institute of Oncology in Leningrad (12) 60 patients with generalized Hodgkin’s disease were treated with nitrogen mustard administered in a chronic fashion. The drug was given initially in 8–16 weekly injections; supplementary radiation therapy and supplementary courses of nitrogen mustard were used if necessary. The 5-year survival rate of this group of patients was significantly better (33%) than a group treated with radiation therapy alone at the same institute (16%). Although the 2 groups were considered clinically comparable, the later figure is somewhat lower than the general experience.

Scott (20) treated 40 patients with generalized Hodgkin’s disease initially with nitrogen mustard; 16 received maintenance therapy with chlorambucil, and 44 did not. The duration of remission in the maintenance treatment group averaged 35 weeks, compared to 11 weeks for the group treated with nitrogen mustard alone. The effect of this program on survival rates was not evaluated.

Fig. 1 shows an interesting clinical trial initiated by the late Dr. Henry Diamond. This patient had bilateral pulmonary infiltration due to Hodgkin’s disease. Treatment with vinblastine was initiated and continued intermittently. In addition she received 1000 r midplane dose of telecobalt irradiation to the left lung. The response was equally good bilaterally, and the duration of remission was also equal for both lungs. Radiation therapy made no significant contribution to the treatment of this episode of the patient’s disease and it may be that for certain cases of pulmonary parenchymal involvement, chemotherapy may be at least as effective as radiation therapy.

Table 1 summarize the conclusions of 10 of the previously discussed studies regarding the efficacy of therapy with alkylating agents plus irradiation versus radiation therapy alone. The differences of opinion are evident for results in the treatment of both early and late Hodgkin’s disease studies. The differing opinions are fairly well balanced between the affirmative and
negative views. It should be mentioned at this point that in none of these studies was the patient population randomized and treated according to protocol in the manner in which we have become accustomed to conduct clinical trials in recent years.

C. Unusual Chemotherapy Approaches

Skipper et al. (22) have formulated a concept of "maximal kill" of neoplastic cells resulting from studies of drug-induced increase in the life-span of mice with L1210 leukemia. Based on this concept programs have been formulated for treating childhood leukemia with sequential administration of chemotherapeutic agents before any chemotherapy-resistant lines of cells developed (7). DeVita et al. (6) at the NIH have devised a program for the initial treatment of Hodgkin's disease with sequential administration of vincristine, cyclophosphamide, methotrexate, and prednisone. In addition radiation therapy was given to patients with Stage I and Stage II disease after chemotherapy. Although the interpretation of their initial results was premature, their therapeutic program is being watched with interest.

In addition to the agents mentioned above, some of the drugs which have been very useful in the treatment of Hodgkin's disease, such as vinblastine and methylhydrazine, have not been evaluated to determine if they could contribute to the management of early Hodgkin's disease, nor has there been sufficient time to conduct trials of these agents as extensive as those afforded nitrogen mustard in the management of generalized Hodgkin's disease.

Occasionally results so striking are seen with the use of nitrogen mustard that one has the feeling that if only the bone marrow depression could be circumvented a potential cure might be on hand. McFarland et al. (14) and Clifford et al. (3) have given patients up to 2 mg/kg of nitrogen mustard followed by infusions of autologous bone marrow. Severe hematologic depression was encountered, and the therapeutic results did not encourage continued use of this procedure. It is possible to overcome the hematologic barrier to the use of nitrogen mustard if the distribution of the drug is limited to the upper part of the body and the marrow in the pelvis is excluded during the 1st 10 min of drug administration. This can be accomplished by temporarily occluding the circulation in the lower half of the body with a balloon catheter in the aorta and a pneumatic tourniquet around the abdomen. This technie, referred to as mid-torso occlusion was devised, evaluated, and discontinued at Memorial Hospital. In a group of 34 patients (2) whose chief manifestations of neoplasia were in the lung or head and neck area, it was possible to achieve an estimated 8 times the conventional amount of nitrogen mustard in the tumor-bearing area with little or no hematopoietic depression. Despite the ability to administer this otherwise lethal dose, the results were generally disappointing and remissions when achieved were not of extraordinary duration.

D. Chemotherapy as Initial Treatment of Complications of Hodgkin's Disease

The rapid onset of action after administration of nitrogen mustard makes it particularly useful in the treatment of certain emergency situations in the course of Hodgkin's disease. Vinblastine, too, has a rapid onset of action and presumably could be used in these circumstances as well. Superior vena caval obstruction is one of these complications. It is common to see a fall of venous pressure and clinical improvement within 12-24 hr after drug administration. With radiation therapy as conventionally employed, it would take considerably longer to effect such an improvement. An additional reason given for using nitrogen mustard in this situation is the reduction of tumor mass without the edema which may be caused by the 1st doses of radiation therapy. However, this has been challenged by some radiotherapists who feel that if irradiation is given initially in large enough doses, this problem may be avoided.

Neurologic Complications. Of 1992 patients with Hodgkin's disease reviewed by Williams et al. (24), 62 patients had cord compression and 59 had cerebral or cranial nerve symptoms for an over-all incidence rate of 6.2%. It is of interest that in such a study done in the prelymphangiogram days 66% of the patients had evidence of paravertebral disease. Only 4.2% had epidural disease alone. As an aside, this suggests that for the most part cord compression may be an avoidable complication in patients who have received sufficient radiation therapy to the lymph nodes along the vertebral column. In the same study the percentage of good results in patients with cord compression treated with radiation therapy alone was 43%. Patients treated with laminectomy and chemotherapy and/or irradiation had a
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70% survival rate, while in those treated with chemotherapy and irradiation favorable results were obtained in 73%. Chemotherapy alone is not advisable; 4 patients so treated had some improvement, but in no case was the outcome considered favorable.

HEMOLYTIC ANEMIA. Another complication in the course of Hodgkin's disease is hemolytic anemia. This has sometimes improved after radiation therapy to the spleen, and occasionally patients will be relieved of this complication after administration of an alkylating agent. In a few patients with hemolytic anemia in the course of lymphomas and leukemias whom we have treated with 6-mercaptopurine a favorable effect was not seen. Adrenal cortical hormones are the form of chemotherapy which has been most effective in treating this complication, and there can be no question that in some patients in whom the hemolytic process was severe, life has been restored to a more normal state and survivals prolonged with the use of these agents.

There are other situations in which the rapid effect of chemotherapeutic agents recommends them as the initial form of therapy. Severe bone pain, pruritus, and high fever in Hodgkin's disease may be rapidly alleviated by the use of alkylating agents. Vinblastine may also be very helpful in these situations. Its onset of action is extremely rapid; patients have reported relief of pain within hours of administration. As a generalization the duration of improvement will be prolonged if the disease can be localized and irradiation used as a supplementary form of treatment.

In the final analysis, how the drugs are employed depends upon one's attitude toward the disease and one's impression of the range of usefulness of these drugs. I think it is fair to conclude that there are still some areas of application of the older agents and many areas of application of the newer ones which await more adequate definition of the role they may play in the optimal management of Hodgkin's disease.

References

Chemotherapy as Primary Treatment

Fig. 1. The radiographic appearance of Hodgkin's disease of the lung before, and 7 months after, treatment with vinblastine. The entire left lung was treated with radiation therapy as well (1000 r midplane dose, Co source). The degree and duration of response in the left and right lungs were equally good.
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