

# THE OVER-ALL PLANNING OF THE TREATMENT OF THE HODGKIN'S DISEASE PATIENT\*

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The management of patients with Hodgkin's disease requires understanding of the natural history of the disease, familiarity with the therapeutic modalities, patience, and sympathy. As soon as the histologic diagnosis has been established, it is wise to formulate a long-range therapeutic plan that not only encompasses the immediate problems but anticipates those likely to arise during the evolution of the disease. If the disease is localized, i.e., Stages I and II and particularly II-A, the patient should be referred to a radiotherapist for a course of intensive, curative radiotherapy with super-voltage radiation. An attempt at curative radiotherapy should be made regardless of the histologic type revealed by biopsy. The delivery of high doses of radiant energy is a highly specialized field and is best carried out in those centers that have the greatest experience. As has been stressed by others, a number of investigators have accumulated evidence which has shown that radiotherapy directed not only to the original tumor but also to contiguous areas not clinically involved significantly improves survival statistics. Thus, Peters and her associates, Easson, and others have shown that radiation to the adjoining lymphatics of

Stages I and II-A improves survival from a 5-year survival of less than 60% of the patients to a 5-year survival of over 70% of the patients. The results with radiation therapy for Stage II-B, the symptomatic regional disease, and for Stage III are not so favorable-less than 20% of patients surviving for 5 years. Kaplan has demonstrated that the recurrence in previously treated areas of Hodgkin's disease is related to the inadequacy of dosage delivered to that particular area. Thus he has calculated that the recurrence rate is decreased to 10% or less if over 3000 rad are delivered to a field involved with Hodgkin's disease. A few years ago, Kaplan embarked upon a more aggressive approach to the treatment of Stage I or Stage II-A Hodgkin's disease, that is disease confined to lymph nodes above or below the diaphragm, or the spleen, or Walden's ring. Advocating that the involved areas as well as all lymph node-bearing areas should be treated, Kaplan has accumulated statistics for Stages I and II cases which appear to be superior to those reported by others whose efforts at radiotherapy are more restricted. Thus, he has increased the 5 year survival rate from 70% to over 80% with his techniques. In addition,

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based upon his experience with these cases, Kaplan has embarked upon a course of treatment for Stage III disease, that is extensive lymphoid involvement above and below the diaphragm, including, at times, the spleen. A preliminary report from his series indicates that his results may be superior to those achieved with any currently available chemotherapeutic agents.

For the patient with symptomatic regional disease, that is Stage II-B, or those with disseminated disease, Stages III and IV, an entirely different approach would generally be used. The majority of these patients will be given systemic chemotherapy. Nitrogen mustard was the first alkylating agent to be employed. It serves as a reference for the new agents which have since been developed. Nitrogen mustard, Mustargen®, is administered intravenously; usually a total dose of 0.4 mg/kg is delivered as a single dose, occasionally it is divided into 2 to 4 daily doses. The toxicity locally, the nausea and vomiting, and the eventual depressing effect on the bone marrow are well recognized and can be prevented by judicious selection of the dose, meticulous intravenous administration, and by premedication of the patient with barbiturates and chlorpromazine. When nitrogen mustard was the only agent available, it was given intermittently whenever an exacerbation occurred. In previously untreated patients with systemic disease, one can expect a remission lasting 2 to 8 months in 60 to 80% of cases. With the appearance of orally administered alkylating agents, such as chlorambucil, it has become customary to induce remissions with nitrogen mustard and maintain these with the oral alkylating agent. A comparison of over a hundred cases by Frei and Gamble indicated the usefulness of maintaining nitrogen mustard-induced remissions with chlorambucil. Whereas only 50% of patients remained in remission 10 weeks after nitrogen mustard alone, more than 50% of patients remained in remission 40 weeks after nitrogen mustard therapy followed by chlorambucil maintenance. Because of the unpleasant complications of nitrogen mustard administration, cyclophosphamide (Cytosan®, Endoxan®) has been advocated in those instances where immediate results are not necessary. Following induction of remission, usually by the intravenous route, the re-

mission so obtained is continued by the administration of oral cyclophosphamide. In addition to the toxicity mentioned under nitrogen mustard, alopecia and hemorrhagic cystitis may occur; the alopecia is reversible when the dosage of the agent is reduced.

For the past four years, a derivative of the periwinkle plant has been available. Vinblastine sulfate is an alkaloid derivative closely related to vincristine. Vinblastine is usually administered intravenously; however, an oral preparation has received preliminary trial. For the intravenous route, 0.15 mg/kg is usually given initially and this is increased by .05 mg/kg every week, until .25 mg/kg per week is reached. It is then continued at weekly intervals, until there is tumor regression or a change in the blood count or other toxicity. The majority of the toxic manifestations are readily reversible when the dosage is reduced. We have studied 16 patients all of whom have had advanced Hodgkin's disease: 3 patients had extensive radiotherapy; two had alkylating agents; and 10 had received alkylating agents and radiotherapy. One patient had failed with methylhydrazine. These sixteen patients were given 17 courses of vinblastine. Three failed to respond and in one the response is uncertain. In the other thirteen courses, however, significant objective improvement occurred. The objective improvement consisted of reduction of fever, lymph nodes, hepatomegaly, splenomegaly, and sedimentation rate and an increase of weight, performance status, and hemoglobin. The mean remission duration, maintained by intravenous vinblastine, was 10 months. One representative patient, who had failed to respond to two alkylating agents and to 6-mercaptopurine at another institution, appeared at our hospital with weight loss and systemic manifestations as well as lymphadenopathy. With vinblastine it was possible to induce and maintain the remission characterized by a decrease in fever, lymphadenopathy, and malaise and an increase in hemoglobin and in weight. The patient is still in remission.

A number of complications of vinblastine therapy have been reported in the literature. These include: leukopenia, thrombocytopenia, nausea and vomiting, abdominal colic, and constipation, occasionally termi-



nating in ileus. Alopecia may occur. Paresthesias, alteration of taste, general, weakness, malaise, and depression have been reported. Occasionally, patients report pain in the affected lymph nodes. The majority of these toxic manifestations are reversible and improve when the next injection is omitted or the dosage decreased.

Recently, Bond *et al.* summarized their results with a new, improved oral vinblastine preparation. Seven of 12 patients with Hodgkin's disease had an excellent or a good response. The toxic manifestations were not dissimilar from those seen with intravenous vinblastine and usually could be controlled with concomitant administration of chlorpromazine. Carbone *et al.*, using intravenous vinblastine, have obtained results which suggest that it may be a better agent for initial chemotherapy than the alkylating agents.

Approximately three years ago, a new class of agents — the methylhydrazine derivatives — became available. N-isopropyl-a-(2-methylhydrazine) - p-toluamide HCl, ibenzmethylzin HCl (Natulan® is the methylhydrazine derivative most commonly used at the present time. This compound does not have cross resistance with the other cytotoxic agents. It has been shown to fragment DNA *in vitro*, probably as a result of the auto-oxidation with peroxide or by hydroxyl radical formation. The compound is administered orally, usually starting with a dosage of 50 mg per day and increasing the dosage over the next few days to 300 mg/day. At this level, the MIH is continued until the appearance of tumor regression or toxicity. The average loading dose in our series was 9.0 gm given over 50 days. The maintenance dosage ranged from 50 to 150 mg/day. We have administered methylhydrazine to 9 patients, all having advanced Hodgkin's disease. All 9 of the patients had failed on radiotherapy and alkylating agents, and, in fact, 7 had failed on the previously discussed vinblastine sulfate study. All 9 of the patients showed objective improvement. This objective improvement was manifest by reduction of fever, lymph node enlargement, hepatomegaly and splenomegaly, and by increase in weight and performance status, as well as a rise in hemoglobin. The mean

remission duration with methylhydrazine was 5 months. Matté, in a large series, has summarized his results with treatment of patients with vinblastine or methylhydrazine and reported approximately a similar remission rate.

A few of the patients with Stage III disease coming to special radiotherapy research centers are given extensive radiation treatment in an attempt to achieve longer remissions and longer survival than has been possible with the chemotherapeutic programs just outlined. Other patients, coming to special chemotherapy study centers, have been given combination chemotherapy to increase the per cent of patients going into remission and in an attempt to prolong remission duration. Combination chemotherapy is based on the fact that by reduction of dosage of each agent, the toxicity of each of these agents can be reduced, whereas the desired goals might still be achieved by the sum total effect of the drugs. The remission rate in patients given single agents, a combination of agents, and quadruple chemotherapy has been studied in an U. S. National Institutes of Health series by Frei *et al.* Although the series is small, it is readily apparent that major benefit may be derived in combination and quadruple chemotherapy, particularly in patients who have had prior treatment. The schedule employed in one such series of quadruple chemotherapy included cyclophosphamide, vincristine, methotrexate, and prednisone.

The adrenal cortical steroids have a limited but definite place in the management of patients with Hodgkin's disease. The constitutional symptoms can be relieved readily and this is particularly important in those patients who cannot tolerate radiotherapy or chemotherapy because of bone marrow depression. Toxic reactions to these potent steroids must be anticipated and prevented. Smaller doses of steroid are useful in the management of hemolytic anemia and of symptomatic thrombocytopenia.

Patients with anemia, who have become symptomatic, benefit from blood transfusions. No attempt is made to bring the hemoglobin level to normal.



When infections occur, the patient is given the appropriate antibiotic as determined from culture and sensitivity studies. It is not advisable to give prophylactic antibiotic therapy. When this is done, infections arise which are resistant to a large number of antibiotics. In patients with hypogammaglobulinemia, gamma globulin may be administered at regular intervals.

Hydration should be vigorous for patients with hyperuricemia as well as for those with hypercalcemia. Fluids may have to be administered intravenously in the early phases of treatment; later, oral intake must be encouraged and at least two to three liters daily should be given. If following vigorous hydration hyperuricemia persists, administration of allopurinol will prevent further accumulation of uric acid and will reduce the hazard of uric acid nephropathy in patients in whom rapid lysis of cells can be expected to occur following effective radiotherapy or chemotherapy. Allopurinol [4-hydroxypyrazolo(3,4-d)pyrimidine, Zylloprim®, HPP] is a potent inhibitor of xanthine oxidase and prevents the conversion of xanthine to hypoxanthine and of the latter to uric acid. Oral administration of 200 to 800 mg allopurinol daily to patients with lymphoma decreases serum uric acid and excretion of urine uric acid. There has been no evidence of renal, hematologic, gastrointestinal, or hepatic toxicity. In a few patients, attacks of gout have been precipitated in the early phase of allopurinol administration; this can be prevented by prior administration of maintenance doses of colchicine. Drug dermatitis has occurred in a small number of cases

Control of pruritus in patients with Hodgkin's disease may pose a difficult or insoluble problem. Control of the underlying disease process offers the best method for obtaining relief of this distressing symptom. Other measures to control the pruritus include the antihistaminics, such as diphenhydramine (Benadryl®), brompheniramine maleate (Dimetan®), or chlorpheniramine maleate (Chlortrimeton®); sedatives, such

as chloral hydrate or phenobarbital; and tranquilizing agents, such as chlorpromazine (Thorazine®).

The treatment of the lymphomas requires systematic analysis in order to provide the patient with the maximal opportunity for clinical cure or optimal palliation. The planning for therapy begins with a precise histological diagnosis. The staging of the disease after the appropriate clinical, laboratory, and radiological studies have been made is then essential before deciding on the therapeutic regimen.

Radiotherapy is indicated for localized and regional disease regardless of the histological type. The treatment must be planned carefully and given in tumoricidal doses. In Stages I and II the first radiotherapy regimen offers the greatest opportunity for success. The internist shares with the radiotherapist the responsibility of seeing that the treatment is well done. In Stage III disease there is a current experimental program of radiotherapy under investigation with the delivery of large doses of radiation to all lymph node-bearing areas and the spleen. It is to be emphasized that this is still a clinical research program and neither the long-term benefits nor the long-term hazards have as yet been assessed.

In symptomatic Stage III and Stage IV disease, chemotherapy is indicated. The antitumor drug armamentarium has been presented.

The inherent properties which will determine the rate of progress of the disease, as well as its susceptibility to treatment, cannot be precisely assessed when the patient is first seen. Until it is proved otherwise, the physician must therefore assume that appropriate therapy will suppress the tumor. It is well recognized that clinical cure is not always achieved, but research in progress in many laboratories throughout the world offers real promise for the future, perhaps within the lifetime of many of these patients.