A Chemotherapy-Radiotherapy Rx Regimen For Children With Stage III Hodgkin’s Disease

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Long-term survival, often tantamount to cure, is now being obtained following energetic therapy in adults with Stage III, A and B, Hodgkin’s disease. In children, over eight years of age, the disease and the tolerance of therapy appear similar to that of adults. Long-term survival should, therefore, be possible in children despite the fact that late effects of irradiation and even chemotherapy may necessitate some modification of the adult treatment plans. As approximately one third of children with Hodgkin’s disease present with Stage III disease, the potential for cure makes it imperative that these children be identified and, in particular, that they be considered separately from children with Stage IV disease.

Staging

The diagnostic work-up for children with Hodgkin’s disease, including a staging celiotomy, has been described by Exelby in this journal.¹ Mandatory and optional items in the work-up at this institution are listed in Table I. A careful physical examination and tabulation of necessary studies provides the investigator with the information required to accurately stage the patient’s disease.

Our method of staging Hodgkin’s disease and the other lymphomas is a four

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stage system which provides for both nodal and extranodal presentations in localized and generalized disease. The system is described in detail in Figures 1A, B, C and D. Illustrations of both nodal and extranodal presentations are provided for each stage. Stages I through IV are further divided according to constitutional symptoms, e.g., Stage IA, no constitutional symptoms; Stage IB, constitutional symptoms such as fever, night sweats, weight loss or pruritus.

**Treatment Regimens for Stage III Disease**

As a general rule, patients with localized disease (Stages I and II) are treated with radiotherapy while those with generalized disease (Stages III and IV) are managed with a combination of radiotherapy and chemotherapy or with chemotherapy alone. Patients with limited Stage IIIA disease can be treated with radiotherapy alone. However, in patients with constitutional symptoms or extensive mediastinal and abdominal involvement, sequential treatment of these regions fails because of the development of symptoms related to local disease and the increasing severity of constitutional symptoms. Patients with Stage IIIB disease were initially given chemotherapy prior to radiotherapy as a means of reducing symptoms as well as reducing the bulk of all tumor for subsequent radiotherapy. Chemotherapy was at first cautious, consisting of a single injection of vincristine sulfate and cyclophospha-

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Fig. 1A. **Stage I.** The disease is limited to one lymphatic region, or to one extranodal site exclusive of liver, bone marrow, or diffuse involvement of the skin, lung, etc. Above, one lymph node region, left side of neck. Below, one extranodal site as thyroid (rare)
Fig. 1B. **Stage II.** The disease is limited to two or more lymphatic regions on one side of the diaphragm. Associated involvement of extranodal sites such as the gastrointestinal tract is considered Stage II disease. Direct invasion of adjacent structures, such as lung, potentially curable with radiotherapy (as opposed to diffuse involvement), is considered Stage II, not Stage III. Left, two or more lymph nodes with or without direct invasion of the lung. Right, one extranodal site and lymph nodes on one side of the diaphragm, i.e., cecum and para-aortic lymph nodes, rare in Hodgkin's disease but commonly seen in other lymphomas.

Fig. 1C. **Stage III.** The disease involves the lymphatic system on both sides of the diaphragm. Left, lymph nodes on both sides of the diaphragm, i.e., mediastinal, para-aortic and supraclavicular nodes. Right, one extranodal site and lymph nodes on both sides of the diaphragm, e.g., cecum, para-aortic and supraclavicular nodes, rare in Hodgkin's disease but more commonly seen in the lymphomas.

Fig. 1D. **Stage IV.** The disease has disseminated beyond Stage III to diffusely involve the lung, liver, bone marrow, skin, central nervous system, etc.
mide, administered as 'cooling' doses. Good drug tolerance led to progressive increases in the intensity and duration of chemotherapy with the objective of treating potential disease in extranodal sites, primarily bone marrow. On the basis of a three year experience with adults, a clinical trial of the chemotherapy-radiotherapy regimen for children was initiated over three and one half years ago.

**Chemotherapy**

To date, no chemotherapy regimen for Hodgkin's disease has proven superior to 'MOPP.' (Fig. 2.) There are, however, several other regimens which are equivalent to 'MOPP' in therapeutic effect. The predictability of a good response to adriamycin therapy in Hodgkin's disease has led to the incorporation of this agent into combination chemotherapy regimens. (Fig. 3.) As with other components of the combination regimens, the duration of adriamycin remissions is short when used as a single agent. Cardiac toxicity has not been a clinical problem when adriamycin has been incorporated into combination regimens; cumulative doses of adriamycin, however, should not exceed 500 mg./M². The 'A-COPP' regimen used at this hospital differs from 'MOPP' in that it calls for 'introductory' doses of adriamycin prior to the course of combination therapy and because it substitutes cyclophosphamide, which is believed to be less damaging to the bone marrow, for nitrogen mustard.

Both 'MOPP' and 'A-COPP' regimens are associated with nausea and vomiting which may be extreme, particularly on days when adriamycin and alkylating agents are administered. At least 30 minutes prior to intravenous drug administration, older children should be given Thorazine 25 mg. by mouth together with Phenergan, 12.5 mg.; younger children are given proportional doses. Thorazine and Phenergan are repeated in four hours; thereafter the medications are given as needed. Both medications may be given rectally if

| Drug                | 1           | 2           | 3           | 8           | 10         | 29         |
|---------------------|-------------|-------------|-------------|-------------|------------|------------|
| Nitrogen mustard    | 6 mg/M² IV  | 6 mg/M² IV  | 6 mg/M² IV  | 1.4 mg/M² IV Not to exceed 2 mg. | Begin | second course |
| Vincristine (Onocovin) | 1.4 mg/M² IV Not to exceed 2 mg. | 100 mg PO | 100 mg/M² PO Days 3-10 | 100 mg/M² PO Days 3-10 | Dose tapered over 3 day period |
| Procarbazine        | 50 mg PO    | 100 mg PO   | 100 mg/M² PO Days 3-10 | 100 mg/M² PO Days 3-10 | Dose tapered over 3 day period |
| Prednisone          | 40 mg/M² Day PO Days 1-10 | 100 mg PO | 100 mg/M² PO Days 3-10 | 100 mg/M² PO Days 3-10 | Dose tapered over 3 day period |

*M² = per meter squared, PO = per os
Nitrogen mustard (6 mg/M²) and vincristine not to exceed 2 mg are injected into the tubing of a running intravenous solution of 5% glucose in distilled water on days 1 and 8 of each course. Procarbazine and prednisone are administered orally. The dose of procarbazine is increased gradually to avoid excessive nausea and vomiting. On the first day, the dose is 50 mg; on the second day, 100 mg; and on days 3-10, the dose is 100 mg/M². Prednisone is administered at the rate of 40 mg/M² on days 1 through 10. Twenty-nine days from the first day of treatment, the second course of chemotherapy is initiated, provided the white blood cell count has recovered to 4000/mm³ and the platelet to 100,000/mm³. The patient should be observed for toxicity of vincristine and prednisone, which is infrequently encountered when chemotherapy is limited to 2 courses.
nausea becomes troublesome or intramuscularly if vomiting is severe. The administration of fluids intravenously after drug administration is beneficial.

Until recently, chemotherapy was usually limited to two or three courses administered prior to radiotherapy. In keeping with current concepts, a period of maintenance chemotherapy, following radiotherapy, appears desirable, if tolerated.

Radiotherapy

Treatment fields for Cobalt 60 consist of: (1) a "mantle"; (2) an upper abdominal field designed specifically to deliver prophylactic therapy to the liver and retrogastric area; and (3) a pelvic field. Fields are treated according to the magnitude and the significance of their involvement; rest periods of six to eight weeks are given between treatment courses to allow recovery of bone marrow function. In patients with reduced tolerance to large volume radiation, the upper torso field is separated into component parts for treatment. (Figs. 4A, B, C and D.) In general, the dose rate employed for the upper torso, including the mediastinum, is 1,000 rads tumor dose/week for a total tumor dose of 4,000 rads to areas with demonstrable disease and 3,000 rads to clinically negative regions. Treatment is administered at 200 rads given dose/day through the anterior "mantle" field; additional dosage from posterior fields is given to effect a tumor dose of 200 rads/day. Dose rates for the upper abdomen and pelvis are 750 rads tumor dose/week for a total of 3,000 rads/four weeks. To prevent radiation nephritis, the tumor dose to the kidneys is limited to 2,000 rads by shielding these organs posteriorly from the beginning of treatment with two half-value layers of lead. To prevent radiation hepatitis, the dose to the liver is limited to 2,500-3,000 rads in four weeks. Boosts of 1,000-1,500 rads tumor dose may be used to supplement positive areas in the axilla, neck, paraaortic and iliac regions. Boosts are not
Figs. 4A, B, C and D. **Upper torso.** In general, an anterior "mantle" supplemented by posterior mediastinal, axillary and cervical fields is employed for combinations of definitive and prophylactic treatment. **Lower torso.** The abdomen and pelvis are frequently treated sequentially. For Cobalt 60, two half-value layers of lead are placed over the kidney posteriorly from the beginning of treatment. An alternate approach would be to treat the major regions separately in any desired combination depending on the local and the systemic tolerance.
given to the mediastinum because of the heart's and spinal cord's limited tolerance to irradiation.

Abdominal irradiation is always associated with radiation sickness and antiemetics should be given on a regular schedule including Saturdays and Sundays (when radiation therapy is not being given) to minimize nausea and prevent vomiting. Doses of Thorazine and Phenergan, as described previously, should be given 30-45 minutes before meals. Both the child and the parent should be questioned repeatedly regarding diarrhea, which must be controlled to prevent dehydration and to maintain body weight. After each loose stool, older children should be given Donnagel PG, one tablespoon, by mouth; younger children are given proportionately smaller doses. Even minimal dehydration should be corrected promptly with intravenous fluids.

Results

Pooled results for adults and children with Stage III Hodgkin's disease treated with a chemotherapy–radiotherapy regimen have been encouraging. Four-year survival figures exceed 60 percent for both Stage III A and III B disease. (Fig. 5.) Adults and children in this study received varying amounts of chemotherapy. Treatment data and survival for five children treated with "MOPP" chemotherapy prior to radiotherapy are shown in Table 2. Prior experience using radiotherapy alone in the treatment of two older children with minimal Stage III A disease showed that a time period of six to seven months was required for completion of radiotherapy. The addition of two full courses of "MOPP" to the treatment plan did not significantly prolong treatment beyond the time required for chemotherapy. However, more intensive chemotherapy

![Fig. 5. COMBINED CHEMOTHERAPY AND RADIOTHERAPY SURVIVAL](image_url)

No statistically significant difference is noted in the four year survival figures for Stage III-A, i.e., 64 percent versus Stage III-B, 68 percent (P = .91).
| Patient and Stage | Treatment Plan | Time to Completion (days) | Dosages T.D. Rads; % of Planned HN₂ and Procarbazine | Survival from Diagnosis (mo) |
|------------------|----------------|--------------------------|--------------------------------------------------|-----------------------------|
| E.K., III-A      | 2(MOPP) → XRT(P-UA-M) | 246                      | HN₂ 100%, Pro 100%                               | 42½⁺ NED                    |
|                  |                |                          | P = 3000                                         |                             |
|                  |                |                          | UA = 3000                                        |                             |
|                  |                |                          | M = 3000                                         |                             |
| E. L., III-B     | 2(MOPP) → XRT(P-UA-M) | 222                      | HN₂ 100%, Pro 100%                               | 41½⁺ NED                    |
|                  |                |                          | P = 3000                                         |                             |
|                  |                |                          | UA = 3000                                        |                             |
|                  |                |                          | M = Med 3500                                     | Neck 4500                   |
| K.W., III-A      | 2(MOPP) → XRT(M-UA-P) | 225                      | HN₂ 100%, Pro 100%                               | 33½⁺ NED                    |
|                  |                |                          | M = Med 3500                                     | Sc 4500                     |
|                  |                |                          | Sc 4500                                          | Neck R 4000                 |
|                  |                |                          | Sc 4500                                          | L 3000                      |
|                  |                |                          | UA = 3000                                        | P = 3000                    |
| S.C., III-A      | 3(MOPP) → XRT(M-UA-P) | 363                      | HN₂ 100%, Pro 100%                               | 25½⁺ NED                    |
|                  |                |                          | M = 3500                                         | UA = 3500                   |
|                  |                |                          | UA = 3500                                        | P = 3000                    |
|                  |                |                          |                                               |                             |
| H.M., III-A      | 6(MOPP) → XRT(UA-P-M) | 364                      | HN₂ 80%, Pro 80%                                 | 13½⁺ NED                    |
|                  |                |                          | UA = 3000                                        | P = 3000                    |
|                  |                |                          |                                               | M = 4000                    |

M = mantle; UA = upper abdomen; P = pelvis; Sc = supraclavicular; L = left; R = right
HN₂ = nitrogen mustard; Pro = procarbazine;
NED = no evidence of disease
in one child (three courses of "MOPP") resulted in an undue prolongation of the total period of treatment.

Reduction of dosages of the myelosuppressive agents—nitrogen mustard and procarbazine—was necessary in one child treated with six courses of "MOPP." All children in this group are surviving free of evidence of Hodgkin's disease from 13 to 42 months.

An overzealous treatment plan in two instances was not completed. (Table 3.) Failure can be attributed to premature initiation of radiotherapy which did not allow for recovery from myelosuppression following chemotherapy and to an attempt to treat the entire abdomen in one course of radiotherapy.

"A-COPP," used in two patients, appears to be well tolerated provided sufficient time is allowed for recovery of bone marrow function before instituting radiotherapy. The projected time required for completion of this treatment regimen is 18 months. (Table 4.)

**Discussion**

The chemotherapy–radiotherapy regimen for adults with Stage III Hodgkin's disease can be completed successfully in older children and survival appears to be excellent. Effects of this treatment on growth and maturation cannot be determined at this time. Girls receiving such therapy will not be able to bear children; boys will probably be sterile. However, as the potential for cure is quite real, this therapeutic regimen can be recommended for children over 10-12 years of age, provided the probability of sterility is accepted.

On the other hand, such a treatment regimen for younger children is questioned since the risks of radiotherapy become greater with decreasing age. Effects of chemotherapy on growth appear to be temporary; the effects on child-
Dosages

Patient and Stage Treatment Plan Time to Completion (days) Dosages (Rads; % of Planned Chemotherapy) Survival from Diagnosis (mo.)

I. II.s + 10'/2+ GH, 2 (A-COPP) 274+ Adr 100%, Cyt 100% Pro 100%

Ill-A +4 (A-COPP) Adr 100%, Cyt 100%, Pro 100%

MM. 163+ 4%+ III-A 2 (A-COPP) XRT (M-UA-P) M - 3000 UA - 3000 P - 3000 UA - In progress

— = Mantle; UA = upper abdomen; P = pelvis; Adr = Adriamycin, Cyt = cyclophosphamide (cytoxan); Pro = procarbazine

In March 1973, a Workshop on Stage III Hodgkin’s disease in children* considered the various therapeutic approaches and all participants expressed concern with the quality of life as related to survival. Limiting radiotherapy to gross disease only and relying on chemotherapy to control occult disease was viewed favorably by the participants, even though the potential for cure—which is unknown at this time—may be reduced when compared to the radiotherapy—chemotherapy regimen described.

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