Hodgkin’s Disease in Childhood

By Robert C. Young, Vincent T. DeVita, and Ralph E. Johnson

Thirty-eight children with Hodgkin’s disease have been treated over the past 8 yr with either intensive radiotherapy or combination chemotherapy (MOPP), depending on their initial stage. The median survival of the entire group of children has not yet been reached, as 63% are still alive, but it will be in excess of 58 mo. Median survivals by stage are as follows: stage I, greater than 46 mo; stage II, greater than 46 mo; stage III, 35 mo; and stage IV, 26.7 mo. Although the numbers of children are small, these results appear significantly superior to published reports utilizing less intensive radiotherapy and single-agent chemotherapy and suggest that intensive radiotherapy for localized disease and combination chemotherapy for advanced disease may, at present, be the preferred forms of therapy for Hodgkin’s disease in childhood.

HODGKIN’S DISEASE is not a common illness in childhood in the United States, although it is frequently seen in the pediatric age group in other countries. Nevertheless, the disease does occur in all age groups from childhood to far-advanced old age, and even in the United States, the pediatric age group is not spared. Since the disease is uncommon in childhood, few centers have been able to collect information on a uniform therapeutic approach to the treatment of all stages of the disease. In addition, there is little information available on the survival of pediatric patients after treatment with intensive radiotherapy for early stages and with combination chemotherapy for advanced Hodgkin’s disease. Since 1964, we have been using wide-field (extended field or total nodal) irradiation in the management of all patients with stages I, II, and III disease and a combination chemotherapy program (MOPP) for all patients with stages IIIB and IVB disease. This report summarizes our experience with intensive radiotherapy and combination chemotherapy in Hodgkin’s disease in childhood.
MATERIALS AND METHODS

Patient Selection

Since 1964, 38 children, age 16 yr or under, have been treated at the Radiation and Medicine Branches of the National Cancer Institute (NCI). Twenty of the 38 children were found to have stage I, II, or IIIA disease and were treated with one of the intensive radiotherapy regimens, as was a single child with stage IIIB disease. None of these 21 children had received prior therapy. Seventeen children were found to have stage IIIB or IV disease, and 14 of these had not received any therapy prior to their referral to the NCI. The three additional children in the chemotherapy series had relapsed from intensive radiotherapy but had not received any chemotherapy and were entered directly on to the combination chemotherapy program.

Histology

All children had biopsy-proven Hodgkin's disease confirmed before entry into the study. Without knowledge of the clinical status of the patient, the biopsy specimens were classified by the histologic criteria of Lukes and Butler. This classification was modified to include subcategories of the nodular sclerosis group as lymphocyte-predominant, mixed cellularity, or lymphocyte-depleted.

Staging

Clinical staging was performed during the initial evaluation, and children were classified according to the Rye staging classification. History, physical examination, complete blood counts, liver function tests, and chest roentgenograms were routinely performed. In addition, whole chest tomography was performed when mediastinal disease was present. A metastatic bone series and lymphangiography were performed on all children, and bone marrow biopsies with a modified Vim-Silverman marrow biopsy needle were routinely done. Strontium bone scans were performed on children who had systemic symptoms, appropriate blood chemistry abnormalities, or evidence of bony involvement. Laparotomies were not used for staging in this series, but several children had peritoneoscopy. The diagnostic criteria for organ involvement have been outlined in detail in other publications and were essentially unchanged in the present study. Twelve children had stage IV disease with the following organ involvement: four had lung alone (two biopsy proven), two had liver alone (one biopsy proven), three had bone alone (two biopsy proven), and three had multiple organs involved (two biopsy proven).

Radiotherapy

The children included in the radiotherapy portion of the present study were a part of a prospective comparison of extended field vs. total nodal irradiation (TNI) for patients with stage I-II disease and of TNI for stage III involvement. Age did not influence entry into this study, and the children were treated with techniques and tumor doses (3500-4000 rads) identical to that employed for adult patients. A split-course program of administering the 4000 rads tumor dose over an elapsed time of 6-8 wk was found to be effective therapeutically but attenuated the acute and delayed radiation effects on normal tissues.

<table>
<thead>
<tr>
<th>DAYS</th>
<th>1</th>
<th>2</th>
<th>7</th>
<th>8</th>
<th>9</th>
<th>14</th>
<th>28</th>
</tr>
</thead>
<tbody>
<tr>
<td>VCR</td>
<td>1.4</td>
<td></td>
<td>1.4</td>
<td></td>
<td></td>
<td>No Therapy</td>
<td></td>
</tr>
<tr>
<td>HN2</td>
<td>6</td>
<td></td>
<td>6</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Procarbazine</td>
<td>100</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prednisone*</td>
<td>40</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Cycles 1 and 4 only

Fig. 1. Outline of a single cycle of combination II chemotherapy (MOPP).
If WBC count before starting new course was
>4,000 100% of all drugs
3,999-3,000 100% of vincristine, 50% nitrogen mustard and procarbazine
2,999-2,000 100% of vincristine, 25% nitrogen mustard and procarbazine
1,999-1,000 50% vincristine, 25% nitrogen mustard and procarbazine
999-0 No drug

If platelet count before starting new course was
>100,000 100% of all drugs
50,000-100,000 100% vincristine, 25% nitrogen mustard and procarbazine
<50,000 No drug

Combination Chemotherapy

The combination chemotherapy consisted of the intermittent administration of vincristine sulfate, procarbazine hydrochloride, nitrogen mustard, and prednisone. Figure 1 illustrates a single cycle of the regimen. The treatment was administered in monthly cycles for a total of six treatments. Vincristine and nitrogen mustard were given as rapid intravenous injections on days 1 and 8 of each cycle. From days 1 through 14, oral procarbazine and prednisone were given, but prednisone was only given on the first and fourth cycles. Children were staged and often received their first course of therapy in the hospital but, thereafter, usually received the remainder of their therapy as outpatients. Each cycle took approximately 1 mo, and the subsequent courses of treatment were regulated by the hemopoietic recovery at the time the subsequent course was to be administered. A sliding scale was used to determine the subsequent dose, as shown in Fig. 2.

Evaluation of Response to Treatment

Children were evaluated as to the status of their disease at the completion of radiotherapy or, in the case of chemotherapy, at the end of six cycles. If any evidence of disease remained, the children were considered remission induction failures. Complete remission was judged to be present when all of the patient’s complaints, physical examination, performance status, and laboratory and roentgenographic studies had returned to normal. Areas of known involvement before therapy were reexamined post-treatment before the child was designated in complete remission. Statistical analysis of the survival data was performed by Dr. Richard M. Simon, National Cancer Institute.

RESULTS
Characteristics of the Entire Patient Population

Of the 38 children with Hodgkin’s disease, 28 (74%) were males, and 10 (26%) were females. The details of the patient population are shown in Table 1. Forty-five per cent of the entire group of children presented with advanced stages of disease requiring chemotherapy. Stage IVB was the most common single stage seen in the over-all series, and almost one-third of the children presented with this advanced form of Hodgkin’s disease. Fifty-five per cent of the entire group of children had disease suitable for intensive radiotherapy.

The histologic characteristics of the entire group are also listed in Table 1.
Table 1. Hodgkin’s Disease in Childhood: Characteristics of Treatment Group 38 Children

<table>
<thead>
<tr>
<th>Sex</th>
<th>Stage (at Rx)</th>
<th>No. of Children</th>
<th>(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>28 Males (74%)</td>
<td>IA</td>
<td>7 (18)</td>
<td></td>
</tr>
<tr>
<td>10 Females (26%)</td>
<td>II A</td>
<td>8 (21)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>II B</td>
<td>3 (8)</td>
<td></td>
</tr>
<tr>
<td>Age—Mean 13 yr. Range (6–16)</td>
<td>III A</td>
<td>3 (8)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>III B</td>
<td>5 (13)</td>
<td></td>
</tr>
<tr>
<td>No. of Patients Age</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>6</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>7</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>9</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Histology No. of Children (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>10</td>
<td>Lymphocyte-predominant (LP)</td>
<td>9</td>
</tr>
<tr>
<td>1</td>
<td>11</td>
<td>Lymphocyte-depleted (LD)</td>
<td>4</td>
</tr>
<tr>
<td>3</td>
<td>12</td>
<td>Mixed cellularity (MC)</td>
<td>10</td>
</tr>
<tr>
<td>6</td>
<td>13</td>
<td>Nodular Sclerosis</td>
<td>15</td>
</tr>
<tr>
<td>6</td>
<td>14</td>
<td>LP</td>
<td>2</td>
</tr>
<tr>
<td>4</td>
<td>15</td>
<td>LD</td>
<td>3</td>
</tr>
<tr>
<td>11</td>
<td>16</td>
<td>MD</td>
<td>8</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Diffuse fibrosis</td>
<td>2</td>
</tr>
</tbody>
</table>

Nodular sclerosis was the most common histologic pattern seen in the children (40%). Lymphocyte-predominant and mixed cellularity patterns appeared with approximately equal frequency (24% and 26%), but lymphocyte depletion was the least common pattern in our children and occurred in only 10%.

Toxicity of the Treatment Programs

Radiotherapy. Despite the intensive radiation therapy, the toxicity associated with its administration was not of a deterrent magnitude. Transient nausea, anorexia, and mucosal reactions commonly were experienced but resolved rapidly after completion of therapy. Hematopoietic function recovered promptly with respect to peripheral blood counts. One male patient, aged 12 yr, had cessation of growth shortly after treatment and was found to be markedly hypothyroid. Resumption of growth has occurred with exogenous thyroid replacement therapy.

Other major complications were limited to two patients who required pericardiectomy for radiation pericarditis and effusion. This problem is now appreciated to be readily avoided with adoption of more protracted dose schedules (e.g., 4000 rads administered in 5–6 wk) and parallel opposed mediastinal fields.

Growth inhibition secondary to extensive skeletal irradiation has not proven a complication of sufficient magnitude to contradict such a therapeutic approach in potentially curable patients. It is important to emphasize that some consistent reduction in the vertebral body volume has been observed in the younger children, especially those below the age of 12. However, absence of radiation exposure to the epiphyses of the long bones has allowed an over-all growth rate that approximates the genetically anticipated stature in surviving patients. Careful attention to the shaping of ports avoiding unnecessary inclusion of epiphyseal sites not approximated by disease will minimize these
problems in long bones, but growth centers in the vertebrae must necessarily be included in radiation ports.

**Combination chemotherapy.** Children did not prove to be more or less sensitive to the MOPP regimen than adult patients. There were no drug-related deaths in the children in the present series. Nausea and vomiting were usually present to some degree in all children and tended to be more severe on days 1 and 8 of the cycle after the nitrogen mustard, but these symptoms could be modified by the administration of sedatives, antiemetics, or both. Some children tolerated each cycle increasingly well, while others tended to develop more severe vomiting with each cycle of therapy. In some of the symptomatic children, the rapid disappearance of symptoms and regression of tumor tended to outweigh the side effects of drug administration. Alopecia and neurotoxicity were common complications of vincristine administration, but both were reversible. Constipation and abdominal pain were also seen after vincristine therapy, as was temporomandibular joint pain. In no instance were children bedridden or forced to stay hospitalized because of these effects, and all 17 children remained ambulatory throughout their treatment unless limited by their Hodgkin's disease. Bone marrow suppression was the dose-limiting toxicity of the combination therapy in children, as it was in the adult patients, and the agents toxic to the bone marrow (nitrogen mustard and procarbazine) often had to be reduced progressively with each cycle, as dictated by the sliding scale.

**Response**

**Radiotherapy.** The long-term survival of the 21 pediatric patients treated with wide-field radiotherapy is shown in Fig. 3. Ten of the 21 children treated with radiotherapy have relapsed, and, of these, six have died. Four children who relapsed from 10 to 42 mo after completing radiotherapy remain alive on
chemotherapy. Relapses were seen with approximately equal frequency in each of the histologic patterns and stages, and relapse did not correlate with any particular age within the pediatric age group.

Eleven of the 21 children (52%) who received radiotherapy are still in their initial remission. Of the ten children who relapsed, the mean time to relapse was 21.8 mo (range, 2–42 mo). The mean survival of those six children who died was 28.7 mo, and the mean time to death after the initial relapse was 12.8 mo.

Combination chemotherapy. Details of the response to MOPP chemotherapy are listed in Table 2. Nine children (53%) achieved a complete remission after six courses of MOPP, and the mean time to complete remission was 3 mo. In addition, six children (35%) responded with greater than 50% reduction in tumor masses but failed to achieve complete disappearance of tumor. Two children achieved only minimal tumor response, and regrowth of lesions was apparent during therapy.

Of the eight children who failed to achieve complete remission, six had stage IVB disease and two had IIIB disease. Pulmonary lesions proved most difficult to eradicate, and three of the six induction failures had lung involvement, as

<table>
<thead>
<tr>
<th>Table 2. Hodgkin's Disease in Childhood: Response to MOPP Chemotherapy in 17 Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete remission</td>
</tr>
<tr>
<td>Responded but failed to enter complete remission</td>
</tr>
<tr>
<td>No response</td>
</tr>
<tr>
<td>Deaths during treatment</td>
</tr>
<tr>
<td>Mean duration to complete remission</td>
</tr>
</tbody>
</table>

Fig. 4. Duration of initial complete remission after combination chemotherapy in advanced Hodgkin's disease in childhood.
HODGKIN'S DISEASE IN CHILDHOOD

Table 3. Advanced Hodgkin's Disease in Childhood: Response to Chemotherapy in 17 Patients

<table>
<thead>
<tr>
<th>Complete remission</th>
<th>53%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median duration of initial remission</td>
<td>26.4 mo</td>
</tr>
<tr>
<td>Median duration of survival</td>
<td></td>
</tr>
<tr>
<td>Entire group</td>
<td>33.7 mo</td>
</tr>
<tr>
<td>Nonremitters</td>
<td>11.5 mo</td>
</tr>
<tr>
<td>Complete remitters</td>
<td>36+ mo</td>
</tr>
<tr>
<td>70% of complete remitters alive at 36 mo</td>
<td></td>
</tr>
</tbody>
</table>

well as involvement with other organs. In contrast, all three patients with bone involvement achieved a complete remission.

Three of the children had received prior intensive radiotherapy and, at the time of initiation of chemotherapy, one had IIA and two had stage IVB Hodgkin's disease. All three achieved a complete remission on chemotherapy.

Neither the child's age within the pediatric age range nor histologic classification influenced the frequency of induction of a complete remission.

The duration of the initial complete remission can be seen in Fig. 4. The median duration of initial remission is 26.4 mo. On the other hand, six of nine children (67%) remain in their initial remission from 9 to 66 mo after completion of therapy, although one has died from a second malignancy at 36 mo. Autopsy revealed no evidence of Hodgkin's disease.

Survival data are summarized in Table 3. The median duration of survival for the entire group is 33.7 mo. Six of the eight children who failed to achieve a complete remission have died, and the median duration of survival of the non-
remitters is 11.5 mo. The two induction failures still alive are on other chemotherapy, 18 and 51 mo after failing MOPP therapy.

The median survival of the nine children achieving a complete remission has not been reached, as only two patients in this group have died, and only one from Hodgkin's disease. The median will be greater than 36 mo, as 70% of the children remain alive at 36 mo after completion of therapy. Life-table analysis of the survival of the entire group, the nonremitters and complete remitters, appears in Fig. 5. Three children achieving complete remission have relapsed, and all three did so within the first 18 mo after therapy (at 3, 12, and 18 mo).

*Over-all Survival*

The over-all survival of the entire group of children with Hodgkin's disease is shown in Fig. 6. The median survival has not yet been reached, as 63% of the children are still alive, but it will be in excess of 58 mo. Fifty-seven per cent of the children are still alive 46 mo after therapy. Survival of the patients by stage is shown in Fig. 7, and radiotherapy and chemotherapy patients are combined. Median survival of stage I children will be in excess of 46 mo, as six of the seven are still alive in their initial unmaintained remission. For stage II children, the median survival has also not been reached and will be in excess of 46 mo, as 66% of the children are still alive at 46 mo. For stage III patients, the median survival is 35 mo, and for stage IV patients, the median survival is 26.7 mo.

*DISCUSSION*

Hodgkin's disease in childhood displays certain characteristics that differ significantly from the disease when seen in the adult population. Its incidence increases progressively with age throughout the pediatric age group and into young adulthood, but it is extremely rare in the very young. In fact, the authors...
of a recent review were unable to find a convincing report of a case below the age of 3 yr. There is a marked preponderance of males in childhood Hodgkin's disease and this preponderance only begins to diminish from age 12 upward, indicating perhaps a transition into the pattern of the disease in young adults. Our series of patients, although a referral population, proves to be no exception and shows a marked male preponderance (74%), even though there were only six children below the age of 10. In a recent study of Hodgkin's disease in the first decade of life, the male preponderance was even more marked, with 91% of the 35 patients studied being male. The marked sex difference has never been explained but clearly exceeds the 54% male preponderance in the 25–35 age group at the time of the first wave of the bimodal incidence curve and the 63% frequency that occurs in the 50+ age group. Not only are there clear sex differences, but there are also differences in the frequency of histologic types seen in Hodgkin's disease in the pediatric age group as compared to the adult patients. Forty per cent of our children had nodular sclerosing Hodgkin's disease, a figure similar to the frequency in adults. However, in the very young, the preponderance of this histologic type is even more marked. In one study, 63% of children in the first decade of life had nodular sclerosing histology. The histologic patterns of Hodgkin's disease in children also seem to vary from country to country. Two-thirds of our children had either nodular sclerosis or mixed cellularity patterns, a fraction not significantly different from that reported in a series from England, although mixed cellularity was the predominant type seen there. In contrast is the experience in Africa and South America, where several investigators have noted a predominance of lymphocyte-depleted patterns, as well as an increased frequency of the disease in children in general.

Because this disease is uncommon in childhood, there is little published information available as to survival of children with Hodgkin's disease. The authors of one of the few published studies where a uniform approach to radiotherapy was undertaken treated 21 patients with localized disease in stage I and IIA and reported a 62% 5-yr survival with radiotherapy alone. In the same
study, in which both radiotherapy and chemotherapy were given children with advanced disease, only one child of 22 treated was alive 5 yr after the initiation of therapy. The median survival of children with all stages of Hodgkin's disease has been reported to be 2.9 and 2.7 yr, respectively. Certainly, if these figures represent all patients, those with advanced disease must fare extremely poorly.

The median survival of all children in our series has not yet been reached but will exceed 58 mo. The 5-yr survival for those children with localized I and IIA disease treated with extended field or total nodal radiotherapy exceeds 80%. For children with stages II B and III disease treated with intensive radiotherapy, the 5-yr survival is 50%. One of the difficult aspects of Hodgkin's disease in childhood is that more than 40% of the patients present with advanced disease outside the range of curability and, in fact, in this series the most common presenting stage was IVB. However, MOPP chemotherapy produced complete remission in 53% of the children with advanced disease, and the median survival has not yet been reached for the children in complete remission. Only one has died of Hodgkin's disease, and the median survival will be in excess of 36 mo.

Nevertheless, the remission induction rate and the duration of initial complete remission is not as high or as long as with adults. In the latter, 75%-80% achieve a complete remission, and the median initial remission is 36 mo, rather than the 26.4 mo seen in children. The reason for this difference is not apparent. A better initial response rate to MOPP therapy has been seen in children with Hodgkin's disease in Africa, where mixed cellularity histology predominates. In spite of the somewhat lower response rate in children than in adults, it would seem that the MOPP combination offers a better likelihood of lasting therapeutic response in children with advanced disease than any single agent response reported to date.

Although the majority of the children treated with combination chemotherapy had no prior therapy, three had been previously treated with intensive radiotherapy but had relapsed. All three of these children entered a complete remission after chemotherapy, although one child relapsed 12 mo after completion of treatment. This child is still living 38 mo later receiving other agents. Another child died of a second malignancy 36 mo after chemotherapy, with no evidence of Hodgkin's disease. The third child is still in complete remission 9 mo after completion of therapy. These results suggest that good responses may be obtained after radiotherapy, but they may be less frequent and less durable. Certainly, several studies confirm the activity of MOPP after radiotherapy, chemotherapy, or both, but the response rate and the duration fall significantly when prior treatment has been extensive. These observations emphasize the importance of proper staging to initiate appropriate initial therapy.

Normal growth and development is still underway in many of the children, and as yet no striking abnormalities have been apparent in height, weight, long bone formation, and epiphyseal closure.

As emphasized earlier, retardation in vertebral body growth has been noted, especially in younger patients, following high dose irradiation, but no secondary complications of this growth alteration have occurred to date. Alterations in long bone growth have not been observed. In one patient, a distinct slowing of growth rate secondary to radiation-induced hypothyroidism was observed.
indicating the need to measure routinely growth rates of pediatric patients following cervical irradiation. While studies of growth, development, and immunologic competence are still underway in many children treated with radical radiotherapy, major problems that would constitute a deterrent to such treatment have fortunately not been documented. One can, therefore, consider such therapy in the pediatric age group, provided treatment is carefully designed, administered with high energy radiation, and sufficiently protracted dose schedules are employed.

Recent information on the sterilizing effect of long-term combination chemotherapy in males has been reported and should be anticipated and expected in male adolescents so treated. However, because of the dormant state of the spermatogonia in the prepubescent state, drug-induced sterility may be less frequently seen in patients treated while in childhood. The long-term complications of such intensive chemotherapy and radiotherapy are just beginning to be elucidated, but the mere fact that these children are now living symptom-free on no therapy for long enough periods of time to be candidates for long-term complications is an encouraging fact in itself.

REFERENCES


Hodgkin's Disease in Childhood

Robert C. Young, Vincent T. DeVita and Ralph E. Johnson