Twenty-nine patients with biopsy-proven malignant lymphoma of large cell "histiocytic" type were treated with the APO protocol (vincristine, adriamycin, and prednisone). Treatment consisted of two years of therapy with a modified adriamycin-containing acute lymphoblastic leukemia regimen with preventive cranial irradiation and regional radiotherapy (for patients with clinically localized lymphoma). The median age was 13 years (range, two to 20 years). Thirteen patients had localized disease (stage I, II), and 16 had disseminated disease (stage III, IV). The median follow-up is four years (range, seven months to nine years), and Kaplan-Meier estimates of overall and relapse-free survival are 83% and 76%, respectively. No recurrences have been observed in primary or bulk sites of lymphoma in the group of children treated with chemotherapy only. We conclude that the APO protocol, which was modeled after acute lymphoblastic leukemia regimen, combined with regional radiotherapy can produce long-term remissions for children with malignant lymphoma of large cell "histiocytic" type.

Diffuse large cell "histiocytic" lymphomas constitute approximately 15% to 20% of childhood non-Hodgkin's lymphoma. These malignant lymphomas, which were classified as histiocytic type in the original Rappaport classification, have been found to be cytologically, functionally, and immunologically heterogeneous. They commonly present in lymphoid tissue of Waldeyer's ring, the abdomen (gastrointestinal tract, mesentery, and retroperitoneum), peripheral nodal tissue, and extra lymphatic sites, such as bone or brain. Many are apparently derived from B cells and are hence follicular center cell lymphomas in the Lukes-Collins classification, but some have been shown to be of T cell origin, and a very small percentage have been shown to be of true histiocytic origin.

Treatment with combination chemotherapy, including adriamycin, has resulted in long-term disease-free survival in approximately 50% to 60% of adults with diffuse large cell lymphoma. There is only a scant amount of published data concerning treatment results for children with large cell "histiocytic" malignant lymphoma. In this article, we detail the results of therapy for 29 children with documented large cell malignant lymphoma who were entered consecutively into a treatment protocol using adriamycin, prednisone, and Oncovin (Eli Lilly, Indianapolis) (APO).

Materials and Methods

From December 1973 through December 1982, 29 previously untreated children with diffuse large cell "histiocytic" malignant lymphoma were seen at Children's Hospital Medical Center, Dana-Farber Cancer Institute, and the Joint Center for Radiation Therapy. These patients represent 25% of all cases of childhood non-Hodgkin's lymphoma (NHL) during that time period. Biopsy material was classified according to a modification of the Rappaport classification or the Lukes-Collins classification. Biopsy material from 1973 to 1976 was retrospectively classified by Dr Zebulon Vance (New England Deaconess Hospital). All subsequent cases have been reviewed by one of us (EEL). There were 18 males and 11 females. Their ages ranged from two to 20 years (median 13 years).

Staging

Prior to the initiation of therapy, all children underwent a clinical staging evaluation. This included a history and physical examination, complete blood count, platelet count, sedimentation rate, tests of renal and hepatic function, iliac-crest bone marrow aspiration and biopsy, roentgenogram of the chest, and an abdominal ultrasound study. When clinically indicated, other selected radiologic studies, including computed tomography and radionuclide scans, were performed. Exploratory laparotomy was not done routinely, although the majority of children with intraabdominal primary tumors underwent surgery for diagnostic purposes. A lumbar puncture for the examination of a cytocentrifuged specimen of spinal fluid was not performed until the time of (CNS) prophylaxis. All patients were assigned a stage according to the Murphy classification (Table 1).

Treatment

The treatment protocol (APO) is outlined in Fig 1. APO was administered for two years. During the first two years of this study, radiation therapy was administered during the remission induction period to those children with regionally limited disease (Murphy stages I and II). The adriamycin dose during induction was reduced by half for these children. During this same period, one child with disseminated lymphoma was treated with radiotherapy to her principal site of disease after achieving a complete remission with APO. After 1975, regional radiotherapy was delayed until week 8 of treatment. Children with wide-spread (Murphy stages III and IV) lymphoma were not treated with radiotherapy to bulk or principal sites of
disease unless necessitated by emergency symptoms or failure to achieve a complete remission with chemotherapy. Total tumor doses of 3,000 to 4,000 rad to regional radiation fields were administered to achieve a complete remission with chemotherapy. Total tumor doses to patients with stages I and II disease, and those with primary malignant lymphoma of bone were treated with a tumor dose of 5,000 to 5,400 rad in five to six weeks. Megavoltage irradiation was used in all cases, primarily with a 4-MV linear accelerator. Field arrangements utilized for specific anatomic presentations have been discussed previously.14

CNS prophylaxis consisted of 2,400 rad in 13 daily fractions over 2½ weeks, administered concurrently with intrathecal methotrexate. After 1975, CNS prophylaxis was omitted for patients with Murphy stage I disease or a completely resected gastrointestinal tract lymphoma.

**Definition of Response and Analyses**

Complete remission was defined as the disappearance of all symptoms and clinical evidence of malignant lymphoma. The duration of remission was measured from the end of the consolidation phase to the first sign of relapse. Survival was derived as the time from initiation of treatment to death. For the purposes of statistical analyses, death in complete remission was considered as relapse. The Kaplan-Meier method was used to estimate the distribution of relapse-free and overall survival.

**RESULTS**

All 29 patients entered on study between December 1973 and December 1982 were evaluable for analysis. The data reported here are analyzed with follow-up complete as of August 1983. The distribution of patients according to the principal site of disease and stage is listed in Table 2. Thirteen of the 29 patients had localized disease (I, II), most frequently in the form of nodal, Waldeyer's ring, or primary bone involvement. The majority of patients with disseminated disease (III, IV) had wide-spread abdominal involvement. Only one patient had bone marrow involvement at diagnosis.

Twenty-eight of 29 patients achieved complete clinical remission at the end of the consolidation phase of the APO protocol. The only patient who was considered an induction failure showed progressive mediastinal enlargement after an initial partial response. One patient with disseminated lymphoma required regional radiotherapy for successful remission induction.

None of the 13 children with localized malignant lymphoma experienced a relapse. Two patients, however, died in complete remission. The first child developed encephalitis three months after treatment began, and the second patient died of an unexplained febrile illness after five years, eight months in remission. There were two relapses among the 16 patients with disseminated disease. Both children had isolated CNS relapses occurring at six and ten months while in clinical remission. Each was subsequently treated with aggressive intrathecal and systemic chemotherapy following CNS relapse. One of these children was treated with craniospinal radiation following a second CNS

**Table 1. A Staging System for Childhood NHL (Murphy Classification)**

<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>A single tumor (extranodal) or single anatomic area (nodal), with the exclusion of mediastinum or abdomen.</td>
</tr>
<tr>
<td>II</td>
<td>A single tumor (extranodal) with regional node involvement. Two or more nodal areas on the same side of the diaphragm. Two single (extranodal) tumors, with or without regional node involvement on the same side of the diaphragm. A primary gastrointestinal tract tumor, usually in the ileocecal area, with or without involvement of associated mesenteric nodes only.</td>
</tr>
<tr>
<td>III</td>
<td>Two single tumors (extranodal) on opposite sides of the diaphragm. Two or more nodal areas above and below the diaphragm. All the primary intrathoracic tumors (mediastinal, pleural, thymic). All extensive primary intraabdominal disease. All paraspinous or epidural tumors, regardless of other tumor sites(s).</td>
</tr>
<tr>
<td>IV</td>
<td>Any of the above with initial CNS and/or bone marrow involvement.</td>
</tr>
</tbody>
</table>

**Table 2. Stage and Location of Primary Tumor**

<table>
<thead>
<tr>
<th>Principal Site</th>
<th>Murphy Stage</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>I</td>
</tr>
<tr>
<td>Head and neck*</td>
<td>2</td>
</tr>
<tr>
<td>Peripheral nodal</td>
<td>2</td>
</tr>
<tr>
<td>Mediastinum/lung</td>
<td>3</td>
</tr>
<tr>
<td>Bone</td>
<td>1</td>
</tr>
<tr>
<td>Abdomen</td>
<td>8</td>
</tr>
<tr>
<td>Other</td>
<td></td>
</tr>
<tr>
<td>Totals</td>
<td>5</td>
</tr>
</tbody>
</table>

*Includes Waldeyer's ring.
relapse, and the other received intrathecal chemotherapy through an Ommaya reservoir. Both children are alive and free of malignant lymphoma for 12 months and three years, respectively, following their last CNS relapse.

The median follow-up was four years (range, seven months to nine years, two months). Figure 2 shows Kaplan-Meier plots of the probability of relapse-free and overall survival. The 6-year relapse-free survival estimate is 76%, and the 6-year overall survival estimate is 83%. There was no statistically significant difference in relapse-free survival for patients with stages I and II (69%) or stages III and IV (86%) (Fig 3).

Twenty-two patients completed all planned therapy (two years), and they have been followed for a median of one year off treatment. There have been no relapses after cessation of therapy.

Toxicity

One patient died during treatment as a result of encephalitis of unknown etiology (presumed viral), and a second patient died more than three years after completing all therapy as a result of a febrile illness of unknown etiology.

Nonfatal toxicity was mainly hematologic. There were an average of two hospital admissions per patient for fever and neutropenia during the two-year treatment course. Toxicity associated with CNS prophylaxis was indistinguishable from that observed for a cohort of children receiving similar prophylaxis for acute lymphoblastic leukemia.

L-Asparaginase toxicity included acute pancreatitis in two patients. No patient has developed clinical evidence of adriamycin cardiomyopathy (the cumulative adriamycin dose was limited to 450 mg/m²). The concurrent administration of chemotherapy and radiotherapy to the head and neck area resulted in mild to moderate mucositis in most patients. There was often an erythematous reaction of the skin and minimal lymphedema during radiation therapy for primary malignant lymphomas in bone.

DISCUSSION

The use of combination chemotherapy programs modeled after regimens designed for treatment of childhood acute lymphoblastic leukemia, together with regional radiation therapy, has greatly improved the prognosis for children with non-Hodgkin's lymphoma. The subgroup of children with diffuse lymphoblastic lymphoma have experienced the greatest therapeutic benefit from such an approach. Children with undifferentiated (Burkitt's or non-Burkitt's) malignant lymphomas have fared less well with similar therapy. Based on data from the APO study, children with large cell "histiocytic" malignant lymphomas also responded favorably to an adriamycin-based acute lymphoblastic leukemia-type protocol. The remission induction phase of the protocol includes vincristine, prednisone, and adriamycin, which is a known effective combination for adults with diffuse "histiocytic" lymphoma. The estimated six-year relapse-free survival of 76% is most encouraging in the APO study and compares favorably with that achieved in the most recent adult series for diffuse unfavorable malignant lymphomas. There were six patients with histiocytic lymphoma treated with the LSA2L2 protocol at Memorial Sloan-Kettering, and 66% survived. The results of APO therapy for children with disseminated histiocytic lymphoma (15/16 patients were stage III) appear superior to either the COMP or modified LSA2L2 regimens used in the Children's Cancer Study Group randomized trial.

In the past, treatment failures for children and adults with large cell malignant lymphoma resulted from inability to achieve initial local control of disease or from early dissemination. Thirteen patients in this
series with clinically localized disease were treated with APO and regional radiation, and none have relapsed. Fifteen of 16 children with disseminated disease achieved a complete remission, and 13 did not receive radiotherapy to primary or bulk sites of disease. No recurrences have been observed in primary or bulk sites of disease in the subgroup of children treated with chemotherapy only.

Patients with stages III and IV disease were not treated with radiotherapy because field sizes would have compromised maximal doses of chemotherapy. Radiation therapy was administered to children with stages I and II lymphoma, because it is effective in achieving local control in childhood non-Hodgkin's lymphoma, and it was sometimes a curative therapeutic modality for limited disease. The question of whether or not patients with early stage large cell lymphoma require regional radiotherapy cannot be addressed from our experience. The results of a recently published study indicated that initial systemic chemotherapy with an adriamycin-containing drug regimen was as effective as the same chemotherapy followed by involved field radiotherapy for adults with localized histiocytic lymphoma. Data from the Joint Center for Radiation Therapy showed more in-field recurrences in patients with localized histiocytic lymphoma who were treated with chemotherapy alone compared to patients treated with chemotherapy after resection or radiotherapy. However, overall survival differences between the two groups were small. The role of involved field radiotherapy added to effective chemotherapy for patients with localized histiocytic lymphoma remains open to investigation.

The routine use of central nervous system prophylaxis represents another controversial area. Unlike children with diffuse lymphoblastic lymphoma who are recognized to have a high risk of primary CNS failure, with or without initial bone marrow involvement, the true incidence of primary CNS relapse for children with large cell "histiocytic" malignant lymphoma is not definitely known. The incidence of CNS relapse, for adults with diffuse histiocytic lymphoma, is low after a clinically complete remission is achieved. When the APO study was initiated in 1973, all patients were treated prophylactically with cranial irradiation and intrathecal methotrexate. After 1975, patients with limited favorable sites of disease were excluded, such as those with stage I nodal and extranodal lymphoma and resected ileal-cecal gastrointestinal tract malignant lymphoma. The remaining children were treated with routine cranial irradiation (2,400 rad) and intrathecal methotrexate. CNS relapse occurred in 2/29 patients (2/16 patients with widespread lymphoma). Although unproven, we suspect that CNS prophylaxis has resulted in a decreased incidence of CNS relapse, and we continue to recommend it, particularly for those patients with widespread malignant lymphoma of large cell or "histiocytic" type.

The duration of therapy remains empiric for patients with malignant lymphoma of non-Hodgkin's type. In this study, two years of therapy were administered, whereas most current regimens for adults with "histiocytic" lymphoma discontinue therapy after six to 12 months of treatment. Interestingly, we have not observed a relapse after the first year of remission.

In conclusion, the APO regimen, including CNS prophylaxis and irradiation to regionally limited disease, has resulted in excellent relapse-free and overall survival for children with large cell "histiocytic" malignant lymphoma. Current issues in optimal management include the role of radiation therapy for regional disease, the duration of therapy, and a better definition of the group of children who are at risk for primary CNS relapse. Future ongoing studies should address these critical issues.

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APO therapy for malignant lymphoma of large cell "histiocytic" type of childhood: analysis of treatment results for 29 patients

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