Combined Modality Therapy of Childhood Non-Hodgkin’s Lymphoma

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Introduction

The survival of children with non-Hodgkin’s lymphoma (NHL) has improved in the recent past through the systematic application of intensive therapy employing involved field radiation plus combinations of drugs. A comprehensive review of combined modality therapy of NHL in childhood has been published recently [9]. Table 1, which outlines the 2-year survival by stage of disease at diagnosis from selected representative series [1, 2, 5, 7, 10, 13], shows that as many as 80%–90% of children with stage I disease are curable with such an approach. Also shown is a remarkably uniform overall success rate of roughly 30% and a depressingly high rate of treatment failures in patients with generalized disease (stages III–IV).

Table 1. The 2-year survival, according to the Ann Arbor classification [3] of stage of disease at diagnosis, from five recent series of children with NHL. Survival is stage dependent

<table>
<thead>
<tr>
<th>No. of patients</th>
<th>Percent surviving</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Stage I</td>
</tr>
<tr>
<td>31</td>
<td>50%</td>
</tr>
<tr>
<td>32</td>
<td>55%</td>
</tr>
<tr>
<td>172</td>
<td>58%</td>
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<tr>
<td>64</td>
<td>92%</td>
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<tr>
<td>25</td>
<td>80%</td>
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</table>

The challenge of management of these children today lies primarily in improvement in results in poor prognosis patients. The prognostic features associated with an unfavorable outcome of therapy in children with NHL have been reviewed [8] and include extensive or generalized disease, particularly involvement of the central nervous system (CNS), diffuse histology, and location of primary tumor within the mediastinum or abdomen. In these poor prognosis patients, in particular, optimal combined modality therapy remains ill-defined. The relative contributions of multiple-agent chemotherapy for induction and maintenance of remission, radiotherapy for known areas of bulky tumor involvement and for prophylaxis of CNS disease and surgery, particularly for primary abdominal disease, require critical testing in the setting of controlled clinical trials.

Therapy for children with localized disease with a good prognosis, such as a completely resected ileocecal tumor, or a localized primary in the head and neck region, is more likely to be crowned with success in achieving long-term survival but no less subject to a requirement for analysis of critical variables contributing to such success. The current tendency in some centers is toward overtreatment of such patients, which courts the hazard of unacceptable acute and late effects of therapy, such as infectious complications, leukoencephalopathy, growth retardation, sterility, second malignancies, etc. For example, NELSON and co-workers [11] determined that, of 40 children with localized resectable gastrointestinal tract tumors

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treated by a combination of modalities, there was not a single instance of CNS disease as the
initial site of treatment failure. In a smaller series, HUTTER et al. [6] made the same observation.
The logical conclusion of such analyses is that children with localized completely resectable
gastrointestinal tract tumors should not receive CNS prophylaxis.
That example merely serves to illustrate the obvious point that childhood NHL is a
heterogeneous disorder, not only in terms of relapse patterns, but also in light of clinicopathologic
analyses and correlations of location of primary tumor, histopathology, blast cell surface markers, etc.
Recognition of such heterogeneity would suggest that the therapy for children with NHL
should somehow reflect and accommodate the variable features of disease exhibited.
Despite this, most regimens in current use [9] treat every child with NHL uniformly. The
LSA-2-L2 protocol developed by WOLLNER et al. is an example, as all children are treated with
a complex ten-drug regimen plus intrathecal methotrexate and radiation to single or multiple
sites [16, 17]. Although the results reported are superior to historical and literature controls, the
series is difficult to compare with others reported [9], and the actual contribution of each of the
many agents employed difficult to assess because concurrent controls, treated adequately but
less intensively, are lacking. Current studies in progress [9] may help to clarify some of the
issues outlined above.
This paper will describe the approach to management of children with NHL at St. Jude
Children's Research Hospital (SJCRH) which bases therapy on a staging system that recognizes
the location of primary tumor and extent of disease. Preliminary results are presented of a
randomized trial in progress designed to evaluate 1) the adjuvant effect of involved field
radiation in poor prognosis patients during induction, in addition to combination drugs and 2)
the influence of cranial irradiation plus intrathecal methotrexate during early remission on the
frequency of CNS disease and the duration of complete remission.

Methods

All untreated patients, aged 18 years or younger, with biopsy-proven NHL of any histologic
type or anatomic presentation are eligible, provided they are not in a leukemic phase of NHL
at diagnosis. For purposes of this study, “leukemia” was arbitrarily defined as presence of
circulating blast cells or more than 25% replacement of marrow with blasts.
Patients are clinically staged on the basis of the usual procedures, including hemogram, bone
marrow aspirate, and percutaneous biopsy, roentgenograms of the chest, skeleton and skull,
IVP, lumbar puncture with cytocentrifuge examination of cerebrospinal fluid, and scans of
liver-spleen, bone, and whole body (67Ga). Patients with head-neck primaries have additional
roentgenograms of the facial bones, mandible, and soft-tissue views of the nasopharynx. Upper
and lower gastrointestinal tract series are performed in patients with abdominal disease.
Bilateral lower extremity lymphangiography is performed in patients whose clinically apparent
disease is supradiaphragmatic but not in patients with mediastinal primaries or obviously
disseminated disease. Staging laparotomy and splenectomy are not performed. On the basis of
this pretreatment evaluation, a stage is assigned (Table 2). Treatment is based on stage of
disease and is outlined in Table 3.
Definitions of complete response, remission, and survival durations are conventional.
Calculations of actuarial estimates of remission and survival are performed by standard
statistical techniques and comparisons of the differences in remission and survival according
to the nonparametric log rank test [12].