Potential for Prolonged Disease-free Survival Following Combination Chemotherapy of Non-Hodgkin's Lymphoma

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The evaluation of the results of CVP and MOPP chemotherapy in 80 patients with advanced stages of non-Hodgkin's lymphoma indicates that 36 (45%) achieved a complete remission. Twenty-eight per cent of the entire group of patients remain free of disease for periods ranging from 4 mo to over 7 yr, with a projected median duration of complete remission of 3½ yr. Significant differences in prognosis relative to histologic categories were found. Well-differentiated and nodular histology were positive determinants for improved median survival, confirming the over-all clinical validity of the Rappaport classification system for the non-Hodgkin's lymphomas. The median survival for patients in the most clinically aggressive subgroups with diffuse histology is inferior to those with nodular patterns or well-differentiated cells. In this study it was demonstrated that it was possible to achieve a significant number of complete remissions even in the most aggressive histologic subgroups using combination chemotherapy, and these responses can be correlated with an extended disease-free survival without further therapy.

The lymphomas are the sixth most common form of cancer, and rank fifth for both males and females as a cause of death from malignancy. In the United States approximately 40% of these cases are Hodgkin's disease. The remaining majority of patients have what are usually referred to in general terms as the non-Hodgkin's lymphomas. The first effective form of therapy identified for these diseases had been x-irradiation, and although some patients can be cured by radiotherapy, a review of the old literature suggests that not more than 10% of all patients with all types and stages of non-Hodgkin's lymphoma were rendered permanently free of disease by x-irradiation. This high failure rate relates to the advanced nature of the disease or unappreciated tumor which is often left outside the radiation field. Chemotherapy has been thought of as, at best, palliative for patients with advanced disease since, with single-agent therapy, few patients achieved complete remission and even fewer were kept free of disease despite continuous drug therapy.
Although a detailed histologic classification scheme for non-Hodgkin’s lymphoma has been available since the work of Rappaport, Winter, and Hicks in 1958,9 the majority of clinical trials continued to be reported using the inadequate and non-specific generic terminology of “lymphosarcoma” and “reticulum cell sarcoma.” Little emphasis has been given to the importance of nodularity, degree of cytologic differentiation, or mixed cellular nature of these tumors, as basic correlates of prognosis. The clinical importance of these histologic parameters has recently been emphasized in a large retrospective series of patients treated with single-agent chemotherapy.9

The subject of this report is the results of combination chemotherapy programs in the treatment of 80 patients with advanced previously untreated non-Hodgkin’s lymphoma, and further, these results are correlated with the Rappaport classification.10

MATERIALS AND METHODS

Eighty patients with non-Hodgkin’s lymphomas completed treatment with combination chemotherapy programs between April 1965 and May 1972; 44 were originally diagnosed as “lymphosarcoma” and 36 as “reticulum cell sarcoma.” The initial response and toxicity of CVP therapy in the first 32 patients with lymphocytic lymphoma have been previously reported elsewhere.11

The original biopsy specimens have been reviewed and reassigned to one of eight histologic classifications based on cell type, cellular differentiation, and nodular or diffuse pattern of involvement (Table 1). Staging procedures routinely employed included lymphangiography unless intravenous pyelography was positive, and bone marrow and percutaneous liver biopsies in addition to biopsy of other apparent sites of extranodal involvement. The extent of disease is designated in terms of pathological stage as outlined by the Ann Arbor Conference.12

Three basic treatment programs were used: CVP, a cyclical combination protocol consisting of cyclophosphamide (400 mg/sq m daily intravenously for 5 days), vincristine (1.4 mg/sq m intravenously on day 1), and prednisone (100 mg/sq m daily orally for 5 days) repeated every 21 days.13 If a complete remission status was achieved after a minimum of four cycles, two additional “consolidation” cycles were administered. In those patients who failed to attain a complete remission, repeated cycles of chemotherapy were given until there was either a complete disappearance of disease, at which time two additional cycles were administered, or until regrowth of tumor occurred. No maintenance drug therapy was given to documented complete remitters with the exception of eight patients with lymphocytic lymphoma who achieved a complete remission in 1970. This group of patients was administered maintenance cycles of CVP chemotherapy every 6–12 wk. The other two basic treatment programs were MOPP, consisting of nitrogen mustard (6 mg/sq m intravenously on days 1 and 8), vincristine (1.4 mg/sq m intravenously on days 1 and 8), procarbazine (100 mg/sq m daily orally for 14 days), and prednisone (40 mg/sq m daily orally for 14 days),14 or a modification, C-MOPP, which substitutes cyclophosphamide 650 mg/sq m on days 1 and 8 for nitrogen mustard.

The detailed clinical features of the patient population comprising each of the histologic subgroups14 are summarized as follows:

(A) Diffuse well-differentiated lymphocytic lymphoma (WDLL): This group included four patients with an approximate median age of 47 yr. All four patients presented with Stage-IV involvement; bone

| Table 1. Non-Hodgkin’s Lymphomas: Distribution of Histologic Subtypes |
|-----------------------------|-----------------------------|
| Nodular | Number | Per Cent | Diffuse | Number | Per Cent |
| Well-differentiated lymphocytic | 0 | 0 | Well-differentiated lymphocytic | 4 | 5.0 |
| Poorly-differentiated lymphocytic (NPDL) | 30 | 37.5 | Poorly-differentiated lymphocytic (DPDL) | 9 | 11.3 |
| Mixed histiocytic lymphocytic (NM) | 7 | 87 | Mixed histiocytic lymphocytic (DM) | 4 | 5.0 |
| Histiocytic (NH) | 0 | 0 | Histiocytic (DH) | 26 | 32.5 |
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marrow was the principal site of extranodal disease in all four without peripheral blood findings of chronic lymphocytic leukemia. All patients received CVP chemotherapy.

(B) Nodular poorly differentiated lymphocytic lymphoma (NPDL): This group includes 30 patients, with a median age of 45 yr. Five patients presented with Stage-III, and 25 patients with Stage-IV involvement. The predominant sites of extranodal involvement included bone marrow, 19; liver, seven; ascites, three. Twenty-nine patients received CVP chemotherapy and one patient was treated with C-MOPP.

(C) Diffuse poorly differentiated lymphocytic lymphoma (DPDL): The group is composed of nine patients with a median age of 45 yr. All nine patients presented with Stage-IV involvement; the principal sites of extranodal involvement included bone marrow, five; and liver, four; gastrointestinal, two. All patients received CVP chemotherapy.

(D) Nodular mixed histiocytic-lymphocytic lymphoma (NM): This group consists of seven patients, with a median age of 47 yr. Three patients presented with Stage-III and four patients with Stage-IV involvement. The sites of extranodal involvement included liver, two; bone marrow, one; pleura, one. The chemotherapeutic programs employed in the treatment of this group included CVP, four; MOPP, three.

(E) Diffuse mixed histiocytic-lymphocytic lymphoma (DM): There were four patients in this category, one with Stage-III and three with Stage-IV involvement: bone marrow and liver, one; bone marrow, one; liver, one. Two patients received CVP and the remaining two received C-MOPP chemotherapy.

(F) Diffuse histiocytic lymphoma (DH): This group was composed of 26 patients with a median age of 47 yr. One patient presented with Stage-IIE disease, six with Stage-III, and 17 with Stage-IV involvement. The principal sites of extranodal involvement included bone (osteolytic lesions), 11, of which two had iliac crest bone marrow involvement; gastrointestinal, three; skin, three; and lung, two. Ten patients received MOPP, 15 patients received C-MOPP chemotherapy, and one patient was treated with the CVP regimen.

One month after completion of chemotherapy, all patients who were considered to be in complete remission were reevaluated for evidence of residual tumor with repetition of staging studies previously abnormal, including bone marrow and hepatic biopsies, and repeat lymphangiography if necessary.

No patient was excluded because of toxicity, incomplete therapy, or insufficient data. Partial remission for the purpose of this study was defined as a 75% reduction but not complete disappearance of all evidence of disease. Complete remission indicates disappearance of all evidence of disease and return to a normal performance status. Duration of remission was calculated from the last day of treatment to the first objective evidence of relapse. Survival was determined from the start of therapy to death. The data was presented by the life-table method of Hill, and life-table curves were compared using the generalized Wilcoxon test. Statistical evaluation of small numbers in various subgroups was performed with 2 x 2 contingency tables and computed according to the method of Yates. (Detailed tabular information on each patient can be obtained by contacting the authors at the National Cancer Institute, Building 10, 12N226, Bethesda, Md. 20014.)

RESULTS

Well-Differentiated Lymphocytic Lymphoma (WDLL)

Two of four patients obtained a complete remission with a remission duration of 22 and 24 mo, and one patient had a partial response. All patients have relapsed but are alive at 23+50+ mo with a median survival of 30+ mo. Despite the inability to maintain a disease-free state, the survival of this small group is significantly better than all other histologic categories (p < 0.05) (Fig. 1).

Nodular Poorly-Differentiated Lymphocytic Lymphoma (NPDL)

Eighteen of 30 patients, 60%, were complete remitters, ten patients had partial remissions, and two patients failed to respond. Four of five Stage-III patients obtained a complete remission. Eleven of 19 patients (58%) with bone marrow infiltration and three of seven with liver involvement obtained a complete response. The median duration of complete remissions is 17+ mo, range of 1-40, in
contrast to a median duration of response of 2 mo for partial remitters. Of the seven patients who remain in complete remission, three have received maintenance chemotherapy. The remaining four are in remission from 10+ to 39+ on no further therapy. The median survival for all patients has not been reached, but will exceed 2 yr, (Fig. 1). The median survival for complete responders is 32+ mo, range of 11–50+ mo (Fig. 2) and 26 mo for partial responders. The difference in survival between complete and partial responders is significant \((p < 0.005)\).

**Diffuse Poorly Differentiated Lymphocytic Lymphoma (DPDL)**

Two of nine patients, 22\%, obtained a complete remission, significantly less than the NPDL group \((p = 0.05)\). The site of extranodal involvement was analyzed in regard to response. Only two of seven patients with bone marrow and one of four patients with liver involvement achieved a complete remission. Three patients had partial responses, and four failed to achieve a 75\% reduction in disease. The two complete responders remain in remission on no therapy at 9+ and 31+ mo, in contrast to a 2-mo median duration of tumor control for partial responders. The median survival of 14+ mo for all patients is significantly less than that for the NPDL group \((p < 0.05)\) (Fig. 1). The survival for the two patients in complete remission is 18+ and 44+ mo. Two of the four patients designated as nonresponders died within 3 mo and one within 7 mo after the institution of chemotherapy without significant reduction of adenopathy. The remaining patient had had a stabilization of his disease without a 75\% reduction in adenopathy, and is alive at 18+ mo.

**Nodular Mixed Histiocytic–Lymphocytic Lymphoma (NM)**

Five of seven patients, 71\%, achieved a complete remission and the remaining two patients had a partial response. All three patients with Stage-III disease
achieved a complete remission. The one patient with bone marrow and one of two patients with liver infiltration obtained a complete remission. The median duration of complete remissions from the end of all therapy is 46+ mo, and only one complete responding patient has relapsed. The median survival for all patients with NM is 34+ mo (Fig. 1). The median survival of complete responders is 55+ mo, with a range of 22 mo to over 6 yr (Fig. 2). The median survival of partial remitters is 13 mo (Fig. 3).
Diffuse Mixed Histiocytic–Lymphocytic Lymphoma (DM)

Two of four patients in this histologic category demonstrated a partial response, and all four patients died within 4 mo after being placed on chemotherapy. The survival of this group of patients is significantly different from that of nodular mixed histiocytic–lymphocytic lymphoma ($p < 0.005$).

Diffuse Histiocytic Lymphoma (DH)

Nine of 26 patients obtained a complete remission, 15 were partial responders, and one patient failed to respond. One patient died of causes unrelated to lymphoma or treatment during the induction phase of therapy. Three of seven Stage-IIE–III patients achieved a complete remission, whereas only two of 11 patients with lytic bone lesions and one of three patients with bone marrow and gastrointestinal involvement obtained a complete response. Neither of the two patients with liver infiltration obtained a complete remission. The median duration of complete remissions is $25+\text{ mo}$, with a range of $4+\text{ to } 79+\text{ mo}$ with no relapses. The over-all median survival of $6\text{ mo}$ for all patients with DH is significantly less than all nodular but not diffuse histologic categories (Fig. 1). In contrast, the median survival of the nine patients in complete remission is $31+\text{ mo}$ with a range of $1\text{ to } 7\text{ yr}$ (Fig. 2).

DISCUSSION

The results of combination chemotherapy with the CVP and MOPP programs in non-Hodgkin's lymphoma demonstrate that a significant proportion of all the patients treated ($28\%$) and $61\%$ of those achieving a complete remission have had disease-free survival lasting from $1$ to over $7\text{ yr}$ after all drug treatment was stopped. Nodular and well-differentiated histology were positive determinants for both response and over-all survival, confirming the clinical relevance of the Rapaport classification, but did not predict for the ability to achieve a long-term disease-free state in individual patients.

In reviewing the histologic material of the present study, a number of considerations regarding placement of patients into the classification scheme were encountered. Patients in whom biopsies at the time of original staging demonstrated two distinct histologic subtypes of lymphoma were given the diagnosis of the subtype considered at the time of the study to carry the more unfavorable prognosis, i.e., histiocytic over lymphocytic; diffuse over nodular. The histologic features of the pleomorphic histiocytic lymphomas and lymphocyte depleted (sarcomatous) Hodgkin's disease can at times be indistinguishable. In particular, the former can demonstrate giant cells that closely simulate the Reed–Sternberg cells characteristic of Hodgkin's disease. In these cases the lymphomas are interpreted as either Hodgkin's sarcoma or pleomorphic histiocytic lymphoma largely on the basis of the point of view of the reviewing pathologist. We and others have classified such cases as pleomorphic histiocytic lymphomas in the absence of unequivocal histologic manifestations of Hodgkin's disease at an earlier time or in other anatomic sites. Between cases of histiocytic lymphoma there were differences in cell size, specific nuclear and cytoplasmic characteristics, numerical abundance of mitotic figures, presence or degree of sclerosis, and other features.
We recognize that these cases can be subdivided further into a number of histologic subtypes, a subject which is currently under investigation.

Recognition of the importance, and eventual acceptance, of such a complex histologic scheme by clinicians who have long used the older terminology of lymphosarcoma and reticulum cell sarcoma must necessarily be based on its relevance to treatment. A recent large retrospective study of the Stanford University experience in non-Hodgkin’s lymphoma, one which treated and maintained on single-agent chemotherapy after radiotherapy was no longer of benefit, has re-emphasized the favorable prognostic significance of nodular histology and correctly emphasized the aggressive nature of the diffuse histiocytic lymphoma.9 The major difficulty encountered in an analysis of the Stanford study is the lack of information on clinical staging of patients or interval between radiotherapy and chemotherapy in the individual subgroup. Since chemotherapy was continuous in this study, it is not possible to assess the ability of the initial chemotherapy to maintain patients in a disease-free state after cessation of treatment.

Several clinical studies have demonstrated the superiority of combination chemotherapy in improving both remission rates and survival of patients with non-Hodgkin’s lymphomas compared to results previously obtained with single agents.11,20–22 In particular, the controlled trial of the combination of cyclophosphamide, vincristine, and prednisone versus cyclophosphamide as reported by Hoogstraten et al.20 demonstrated a doubling of both complete remissions and overall response in both “lymphosarcoma” and “reticulum cell sarcoma” with the combination as compared to the single agent. While this study has all the merits of a randomized controlled trial, the conclusions drawn remain in some doubt because the importance of subclassifying histology was not appreciated at the time the investigation was reported. In addition, the study failed to analyze for the influence of intensity of treatment on survival. It has been assumed the latter parameter correlates with the rate of complete remission, as has been documented in the present study. Other large studies have similarly failed to analyze for the influence of histologic subtypes, express results in terms of clinical stage of disease, or failed to include sufficient numbers of patients with diffuse and nodular histology to allow a difference in response and survival to be detected.11,20–22

The present study demonstrates the necessity of subdividing patients on the basis of detailed histology. The well-differentiated lymphocytic lymphomas would appear to have a long survival independent of remission status. This group of patients may have lymph node histology that is indistinguishable from the diffuse well-differentiated cellular infiltration found in chronic lymphocytic leukemia but with a normal peripheral blood picture, suggesting that the two disorders represent a different clinical expression of the same disease process. It is possible that well-differentiated lymphocytic lymphoma may be treated as effectively with single drugs as with more aggressive combination programs.

The favorable influence of nodular histology on both remission rate and median survival of patients with poorly differentiated lymphocytic lymphoma is apparent from the analysis of the present series of patients. Complete remissions were obtained in 62% of patients with the nodular disease as compared to 22% in the diffuse histology group. Partial responders in both categories had significantly poorer survival than that of the complete remitters.
The present study also demonstrates the importance of separating patients with nodular mixed histiocytic-lymphocytic lymphoma from those with diffuse histiocytic disease when analyzing the results of treatment. The former histologic category carries a more favorable complete response rate, 71% versus 34% for DH. Complete remissions in both subcategories can be directly correlated with an increased extended disease-free survival. To include both histologic groups under the heading of “histiocytic lymphoma” as has been proposed would obscure this distinction and, depending on the mix of patients in a given trial, could convey a false impression of responsiveness or the lack of same.

Diffuse histiocytic lymphoma presents one of the major challenges in lymphoma therapy. In general, patients will demonstrate a deceivingly favorable initial response to treatment that is soon followed by a pattern of rapid relapse during the recovery phases of chemotherapeutic cycles. This leads to an eventual complete refractiveness to therapy and involvement of major organs. In this study, patients were considered complete responders only if they achieved remission and maintained it throughout the duration of the treatment course. Patients with apparent complete disappearance of disease and growth between cycles were scored as partial responders. Only 35% of our patients with DH completed six cycles of chemotherapy in complete remission; however, none of these patients have subsequently relapsed for periods extending to over 7 yr.

This experience with several types of combination chemotherapy in advanced non-Hodgkin’s lymphoma suggests that a small but significant number of patients can be offered a prolonged disease-free survival without maintenance treatment. Further improvements in therapy might be expected with the application of our increasing understanding of the natural history of these diseases in the design of treatment programs, such as the combined use of radiotherapy and chemotherapy in poorly differentiated lymphocytic lymphoma, and the identification and use of new active chemotherapeutic agents in combination.

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