

Therapy for Low-Grade non-Hodgkin's Lymphoma

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Low-grade non-Hodgkin's lymphomas, as defined by the Working Formulation, consist of small lymphocytic, follicular small cleaved cell, and follicular mixed small cleaved and large cell histologic subtypes.⁽¹⁾ These lymphomas comprise approximately 25 percent of newly diagnosed lymphomas in the United States.⁽²⁾ It has been suggested that all lymphomas with a follicular pattern be grouped together, rather than as three separate categories as outlined in the Working Formulation.⁽²⁾ The Kiel classification system classifies these lymphomas into centroblastic-centrocytic or centroblastic categories. The Revised European-American Classification of Lymphoid Neoplasms (REAL) divides most lymphomas with a follicular pattern into three grades of disease corresponding to the number or percentage of large cells.⁽³⁾ An International Non-Hodgkin's Lymphoma Classification Project is currently investigating the ability of hematopathologists to apply the REAL classification.

The difficulties in classification cause problems with interpretation of results of therapy for low-grade lymphomas. Expert hematopathologists may differ in their interpretation of biopsies.⁽⁴⁾ In addition, some reports only include low-grade lymphomas as classified by the Working Formulation, while others report treatment results for all follicular lymphomas. Follicular large cell lymphoma is classified as intermediate-grade histology in the Working Formulation. Some studies have suggested that these lymphomas are curable and have a clinical behavior similar to other intermediate-grade lymphomas.^(5,6) Other studies have suggested that the clinical behavior of all follicular lymphomas is similar.^(7,8) Interpretation of clinical results is also complicated by the inclusion of entities such as mantle cell lymphoma and marginal zone lymphomas that may have different clinical behaviors.^(3,9)

Treatment of Localized Disease

Most patients with low-grade lymphoma will have stage III or IV disease at diagnosis.^(1,10) Nevertheless, approximately 5 to 15 percent of patients will have localized disease and can achieve prolonged disease-free survival with radiation therapy. Relapse rarely occurs in previously-irradiated sites, and patients who have been staged with lymphangiograms and laparotomies have been reported to have better outcomes than less aggressively staged patients.^(11,12) Although staging laparotomy is not routinely performed for patients with low-grade lymphoma, these facts suggest that relapse is due to clinically unrecognized disease rather than from failure of radiation. However, some trials have failed to show a difference in outcome between laparotomy-staged and conventionally staged patients.⁽¹³⁾

Three large trials dealing with localized lymphoma have been reported recently. Investigators from M.D. Anderson reported a ten-year survival rate of 69 percent and a relapse-free survival rate of 56 percent in 144 patients with stage I and II follicular lymphoma.⁽¹⁴⁾ The prognosis was worse for patients older than age 50, although no differences in outcome were observed between patients with stage I or II disease or for

those with follicular large cell histology. Relapse-free survival at 15 years was 60 percent following treatment with radiation and chemotherapy as compared with 35 percent for patients who received radiation therapy alone ($p = 0.008$), although no significant differences in overall survival were observed. Another study from M.D. Anderson evaluated results of therapy for 91 patients with stage I and II low-grade lymphoma.⁽¹⁵⁾ Patients received COP-bleo (cyclophosphamide, vincristine, prednisone, bleomycin) or CHOP-bleo (COP-bleo plus doxorubicin) and involved-field radiation. Overall survival at ten years was estimated at 82 percent, and relapse-free survival was estimated at 73 percent. Patients older than 56 years of age had poorer survival.

The Stanford group reported long-term follow-up data on radiation therapy for 177 patients with stage I and II follicular lymphoma.⁽¹²⁾ Median survival was 13.8 years and fifteen-year overall survival was estimated at 44 percent. Relapse-free survival at fifteen years was estimated at 40 percent. Age greater than 60 was associated with poorer outcome. Patients who received staging laparotomies had significantly better overall survival and relapse-free survival. Patients who received more extensive radiation therapy had superior relapse-free survival, although overall survival was not prolonged.

Other trials demonstrate that the use of radiation therapy for localized low-grade lymphomas is associated with five-year relapse-free survival rates of 50 to 80 percent and five-year survival rates of 70 to 100 percent.^(11,13,16-21) Interpretation of results is complicated by the inclusion of patients with follicular large cell histology in some series as well as by the lack of uniformity in radiation administration.

Interpretation of trials is also complicated by the addition of chemotherapy to radiation in some series. Retrospective analyses have shown that combined modality therapy may be associated with improved relapse-free survival without benefitting overall survival.^(18,21,22) A prospective randomized British National Lymphoma Investigation trial found no improvement in disease-free survival or overall survival when chlorambucil was added to involved-field radiation therapy for patients with localized low-grade lymphoma.⁽²³⁾

Treatment of Advanced Disease

The majority of patients with low-grade lymphoma will have advanced disease at the time of diagnosis. A variety of treatment options are available, and the management of these patients is one of the most controversial areas of oncology. Although these lymphomas are sensitive to radiation and a wide variety of chemotherapeutic agents, virtually all series demonstrate a continuous pattern of relapse with median survival rates of 7 to 10 years.^(7,24-26)

Patients are frequently asymptomatic at diagnosis, and several studies have evaluated the results of a watch-and-wait approach for newly diagnosed patients with low-grade lymphoma.⁽²⁷⁻³¹⁾ Five-year survival in these series ranges from 56 to 83 percent. Patients may frequently be observed several years without requiring treatment if initially managed with this approach. Furthermore, some lymphomas may undergo spontaneous regression.⁽²⁷⁾

A trial from the National Cancer Institute of the United States randomized patients with advanced indolent lymphoma to observation or combination chemotherapy with

ProMACE-MOPP (prednisone, methotrexate, doxorubicin, cyclophosphamide, etoposide, mechlorethamine, vincristine, procarbazine, prednisone) plus total nodal irradiation.⁽³⁰⁾ Disease-free survival was 51 percent following aggressive therapy as compared with 12 percent for patients managed with initial observation ($p < 0.01$); however, overall survival did not significantly differ. It is important to recognize that patients with symptomatic disease were excluded from these trials. Although no impact on survival can be demonstrated, treatment may be more difficult after a delay. In addition, many patients are not willing to accept a watch-and-wait approach after a diagnosis of lymphoma. Nevertheless, this is an appropriate management option for selected patients, particularly those who are elderly or those with coexisting illness.

Numerous treatment options are available for patients with symptomatic disease. Although rarely used, total body irradiation and total lymphoid irradiation may have results similar to chemotherapy for patients with advanced low-grade lymphoma.^(32,33) Single agent chemotherapy with cyclophosphamide or chlorambucil, or combination chemotherapy with CVP (cyclophosphamide, vincristine, prednisone) is effective therapy, although a continuous pattern of relapse is observed without evidence of a plateau in disease-free survival.⁽³⁴⁾

Prospective trials have generally failed to demonstrate the superiority of any particular chemotherapy regimen for low-grade lymphoma when overall survival is used as the endpoint. A randomized French trial failed to show a survival benefit when doxorubicin was added to a regimen of cyclophosphamide, vincristine, procarbazine, and prednisone.⁽³⁵⁾ Other trials of anthracycline-based therapy have failed to show evidence of a plateau in relapse-free survival.^(24,25) A randomized trial at Stanford failed to show significant differences in outcome when single-agent chemotherapy, CVP, and fractionated whole body irradiation were compared.⁽³⁶⁾ The Eastern Cooperative Oncology Group (ECOG) compared cyclophosphamide and prednisone, COPP (cyclophosphamide, vincristine, procarbazine, prednisone) and BCVP (carmustine, cyclophosphamide, vincristine, prednisone) in patients with follicular small cleaved cell lymphoma.⁽³⁷⁾ Although progression-free survival was significantly better with COPP, overall survival was not significantly different. A prospective study from Cape Town failed to demonstrate differences in overall survival in patients with follicular lymphoma randomized between chlorambucil/prednisone and total body irradiation.⁽³⁸⁾

Some studies have suggested a survival advantage for aggressive therapy, however. A regimen of bleomycin, cisplatin, etoposide, doxorubicin, cyclophosphamide, vincristine, and prednisone (BP-VACOP) followed by irradiation to prior sites of disease yielded a four-year survival of 93 percent in a group of 100 patients with low-grade lymphoma,⁽³⁹⁾ as compared with 72 percent for historical controls ($p < 0.02$). A study conducted by the Cancer and Leukemia Group B (CALGB) randomized patients with follicular mixed lymphoma to oral cyclophosphamide or combination chemotherapy with CAVPB (cyclophosphamide, doxorubicin, vincristine, prednisone, bleomycin).⁽⁴⁰⁾ Failure-free survival at 5 years was estimated at 62 percent with combination chemotherapy, compared with 35 percent for patients receiving cyclophosphamide ($p = 0.03$). Overall survival for the groups were 81 percent and 73 percent, respectively ($p = 0.05$). The long natural history of low-grade lymphomas accounts for much of the difficulty in demonstrating a clear survival advantage for any particular treatment option.

Prospective trials are necessary to demonstrate the superiority of any particular regimen if overall survival is considered to be the most important endpoint.

Interferon

Interferon has significant single-agent activity for patients with relapsed and refractory low-grade lymphoma.⁽⁴¹⁾ Several trials have investigated the use of interferon in combination with chemotherapy. A trial by the Groupe d'Etude des Lymphomes de l'Adulte randomized 142 patients with follicular low-grade lymphoma to receive chemotherapy with CHVP (cyclophosphamide, doxorubicin, teniposide, prednisone) or CHVP plus interferon alpha-2b for 18 months.⁽⁴²⁾ The median event-free survival was 19 months for patients receiving only CHVP as compared with 34 months for patients who also received interferon ($p < 0.001$). Overall survival at three years was 69 percent and 86 percent, respectively ($p = 0.02$). A subsequent report noted a median survival of 63.1 months with chemotherapy, and 83.1 months with interferon ($p < 0.001$).⁽⁴³⁾

An ECOG trial randomized patients to COPA (cyclophosphamide, vincristine, prednisone, doxorubicin) or COPA plus interferon alpha-2a.⁽⁴⁴⁾ Although time to treatment failure was prolonged in the interferon arm, no significant improvement in overall survival was observed.⁽⁴⁵⁾ Other phase III trials comparing chlorambucil and chlorambucil plus interferon, as well as CVP and CVP plus interferon, showed improved relapse-free survival with interferon, although overall survival was not improved.^(46,47) A phase III CALGB trial randomized patients with stage III and IV follicular low-grade lymphoma to oral cyclophosphamide or cyclophosphamide plus interferon alpha-2b.⁽⁴⁸⁾ No significant differences in outcome were observed.

Purine Analogs

The purine analogs fludarabine, 2-deoxycoformycin, and 2-chlorodeoxyadenosine (2-CdA) display high single-agent activity against low-grade lymphomas. Phase II trials have demonstrated response rates of 25 to 75 percent in previously treated patients.⁽⁴⁹⁾ A French trial evaluated the use of fludarabine in patients with untreated follicular lymphoma.⁽⁵⁰⁾ The overall response rate among 49 evaluable patients was 65 percent, and the complete response rate was 37 percent. The median progression-free survival was 13.6 months and there was no evidence of a plateau. The Scripps Clinic has reported on the use of 2-CdA in 28 patients with untreated indolent lymphomas.⁽⁵¹⁾ The overall response rate was 89 percent, and 35 percent achieved a complete remission. At three years the relapse-free survival of responding patients was only 17 percent and a continuous pattern of progression was observed.

A trial of fludarabine in combination with mitoxantrone and dexamethasone in patients with recurrent or refractory low-grade lymphoma yielded a response rate of 47 percent and a median failure-free survival of 21 months.⁽⁵²⁾ Other trials have tested the combination of fludarabine and chlorambucil in patients with low-grade lymphoma.⁽⁵³⁾

Monoclonal Antibody Therapy

Monoclonal antibodies may be used in a variety of ways for patients with low-grade lymphomas. Antibodies directed against B-cell antigens and conjugated to radioactive antibodies have been tested in several phase II trials.⁽⁵⁴⁾ High response rates have been observed in pretreated patients and remissions may be durable. Prolonged follow-up will be required to determine how these results compare with other treatments. Other investigators have reported responses with monoclonal antibodies conjugated to toxins⁽⁵⁵⁾ as well as anti-idiotypic antibodies.⁽⁵⁶⁾

Bone Marrow Transplantation

The disappointing results of conventional chemotherapy for low-grade lymphomas have led to trials of high-dose therapy followed by autologous hematopoietic rescue for patients with relapsed and refractory disease.⁽⁵⁷⁻⁶²⁾ Although high response rates are seen and transplantation can be accomplished with low mortality, most series show a continuous pattern of relapse without definite evidence of a plateau in disease-free survival. Follow-up is relatively short in most reports and it is not possible to tell whether patients are cured or if survival is prolonged. The group from St. Bartholomew's hospital noted that relapse-free survival was significantly better than historical controls for patients transplanted in second remission, although overall survival was not significantly different.⁽⁵⁸⁾ A randomized European trial as well as ongoing trials at Dana-Farber Cancer Center and Stanford are evaluating the role of transplantation in first remission.

The lack of a clear plateau in disease-free survival following autologous transplantation for low-grade lymphomas has led to interest in allogeneic transplantation for these patients. The use of allogeneic bone marrow eliminates the possibility of infusing tumor cells and may also take advantage of a "graft-versus-lymphoma" effect. Results from M.D. Anderson show a five-year disease-free survival greater than 50 percent in a cohort of 15 patients following allogeneic bone marrow transplantation for low-grade lymphoma.⁽⁶³⁾ Prolonged follow-up will be required to determine whether patients with low-grade lymphoma are cured with this approach.

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