Symposium article

Follicular lymphoma: Have we made any progress?

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Summary

Follicular lymphomas are characterized by relatively long median survivals and a continuous pattern of relapse. The heterogeneity in these diseases is increasingly appreciated, leading to concerted efforts to define prognostic factors and risk-adapted strategies. The status of multiple options for treatment including interferon, fludarabine, dose intensification with autologous transplantation, therapy targeting the CD20 antigen and novel approaches is reviewed. The long natural history of follicular lymphoma requires mature data for accurate analysis. However, the achievement of molecular remission as a surrogate endpoint is under active investigation.

This is an exciting era for the clinical investigation of follicular lymphoma given the large number of candidate therapies and their potential combinations and permutations. Although the goal of primary treatment remains durable remission and cure, the sequential application of effective, non-cross-resistant treatments may also result in a prolongation of median survival time. It is essential that physicians treating patients with follicular lymphoma demonstrate restraint in the application of new treatments and cooperate in the study of new therapies in carefully designed phase II and phase III trials.

Key words: fludarabine, follicular lymphoma, interferon, Rituximab, stem-cell transplantation

Introduction

Follicular low-grade lymphoma is characterized by a long survival relative to other non-Hodgkin’s lymphomas [1, 2]. Despite initial complete responses to single alkylating agents, combination chemotherapy and combined modality approaches, a continuous rate of relapse has been observed [3, 4]. Survival data for low-grade lymphoma (inclusive of the small lymphocytic subtype) have remained static for nearly three decades [2]. This progress report will evaluate maturing data with a number of alternative approaches including interferon, fludarabine, dose intensification with hematopoietic stem-cell rescue, therapy targeting the CD20 antigen present on follicular lymphoma cells and novel approaches as outlined in Table 1.

Deferred therapy

Selected patients with follicular lymphoma, those who are asymptomatic and have a modest tumor burden, appear to have no reduction in survival when cytotoxic therapy is deferred until disease progression [5]. In 1978 a randomized trial was launched at the National Cancer Institute, testing the concept of deferred therapy or ProMACE-MOPP (prednisone, methotrexate, doxorubicin, cyclophosphamide, etoposide, mustargen, vincristine, procarbazine) chemotherapy and low dose total lymphoid irradiation in diagnosis in selected patients with advanced stage low-grade lymphoma [6]. Although this study has not been published, an update was provided at the Presidential Symposium at the 1997 meeting of the American Society of Clinical Oncology. No differences in overall survival were seen in the two arms of this study. The GELF (Groupe d’Etude des Lymphomes Folliculaires) performed a study in low tumor burden follicular lymphoma in which patients were randomized to deferred therapy, prednimustine or α-interferon [7]. Again, no differences in survival were observed. On the basis of these and other data, the NCCN guidelines for management of asymptomatic low-grade lymphoma recommended deferred therapy [8]. Implicit in the interpretation of these data is the concept that features at diagnosis of follicular lymphoma may be used to direct risk-adapted therapy.

Prognostic factors

Several groups have described prognostic factors for patients with advanced follicular lymphoma. In the GELF schema, patients with any one of the following features were considered to have a high tumor burden: systemic symptoms, elevated LDH, bulky disease site > 7 cm, effusion, three or more Ann Arbor sites each 3 cm or greater, circulating lymphoma cells, cytopenias and splenomegaly [7, 9]. These were validated on a large patient sample. The International Prognostic Factors Index has been applied to the low-grade lymphomas and found to identify subgroups with significantly different prognoses. However, only a small percentage of patients...
fall into the higher risk groups, such that this system of stratification may not be optimal for follicular lymphoma. To that end, an international effort is in place to develop prognostic factors for low-grade lymphoma.

**Interferon**

Interferon has been incorporated into primary therapy of follicular lymphoma in a large number of randomized clinical trials [9–12]. These studies have disparate results, ranging from no difference in outcomes to the demonstration of superior survival when interferon was combined with chemotherapy. Potentially important variables include differences in eligibility criteria (follicular only or diffuse small lymphocytic histologies (mantle cell was included in some series); ‘high risk features’), incorporation of interferon during induction, maintenance or both; differences in the dose, schedule and duration of interferon; and the chemotherapy regimen which ranged from single alkylating agent to more complex combinations including doxorubicin. Because of these differences, the studies are not comparable. However, none of them demonstrate a plateau on the freedom from progression curve suggestive of cure. A meta-analysis of the interferon data was presented in preliminary form and this analysis suggested a benefit for interferon [13]. However, the data from the SWOG (Southwest Oncology Group) study, also presented in preliminary form in 1998, was not included in the meta-analysis [12]. The SWOG randomized patients to ProMACE-MOPP alone or followed by maintenance interferon. No differences in failure-free survival or overall survival were observed in that study.

**Fludarabine**

An overall response rate of 65% and a complete response rate of 37% in previously untreated follicular lymphoma with the purine analog fludarabine was described by Solal-Celigny et al. [14]. The combination of fludarabine, mitoxantrone and dexamethasone was described as a very effective regimen in previously treated follicular lymphoma by Mclaughlin et al. [15]. The ECOG (Eastern Cooperative Oncology Group) performed a phase I–II dose escalation study with the combination of fludarabine and cyclophosphamide. Based on a high complete response rate and an estimated freedom from progression of 80% at three years, ECOG is testing this regimen in a phase III study (see below) [16]. Recently, two interesting studies using fludarabine in untreated patients were reported in preliminary form. The EORTC conducted a randomized clinical trial evaluating fludarabine as a single agent or a low-dose combination of cyclophosphamide (750 mg/m² given on a four week schedule in a randomized clinical trial), vincristine and prednisone [17]. The complete response rate was higher and the time to progression were significantly longer with fludarabine in this study. However, the results are difficult to interpret because the intensity of cyclophosphamide was reduced relative to standard combinations. The combination of fludarabine and mitoxantrone was tested by the SWOG in a phase II trial involving 81 patients (67 follicular histology). The regimen was well tolerated and a 91% response rate was observed; however, failure-free survival at two years was no different that historical controls treated with CHOP or ProMACE-MOPP [18].

**Dose intensification and hematopoietic stem-cell transplantation**

Following the success of myeloablative therapy and autologous hematopoietic stem-cell transplantation in diffuse aggressive lymphoma, investigators applied this approach to follicular low-grade lymphoma. Variables have included eligibility criteria (number of prior prior treatments/relapses, histology, tumor burden at transplant, chemotherapy-sensitive disease), preparatory regimen (chemotherapy only or total body irradiation and chemotherapy), and stem-cell product (purged or unpurged, bone marrow or peripheral blood stem cells). These differences complicate the interpretation of the data and, further, some reports incorporate multiple variables from a single institution or group. In addition, the results from many centers are insufficiently mature to evaluate efficacy and toxicity.

In the series of Freedman et al., chemo-sensitive patients in a minimal disease state were prepared with cyclophosphamide and total body irradiation followed by autologous, purged bone marrow. An update of these data were provided in 1998 at with a follow-up time of eight years [19]. Disease-free survival was 40% and
t(14;18) bearing lymphocytes has been related to time to minimal residual disease. Detection of minimal residual disease in the form of PCR are important investigational avenues. An early report from Gribben et al. suggested that the ability to purge the stem-cell product was predictive of time to tumor progression [24]. Enhanced ability to purge the graft, both in vivo as well as in vitro, and strategies to lower the risk of myelodysplasia or leukemia are important investigational avenues.

**Minimal residual disease**

Detection of minimal residual disease in the form of t(14;18) bearing lymphocytes has been related to time to relapse in serial samples of bone marrow after high-dose therapy and hematopoietic stem-cell transplantation. Evaluation and reporting of these data has contributed to difficulty in assessing their significance. In addition, polymerase-chain reaction (PCR) methodology for the detection of minimal residual disease varies widely among centers. A large series from the M.D. Anderson was updated recently [25]. The ability to achieve a molecular remission at one year, defined as the absence of t(14;18) bearing lymphocytes, was highly predictive of failure-free survival at X years, 73% for PCR-negative and 28% for PCR-positive. Application of the landmark analysis is an important feature of this report. The ability to perform quantitative, real-time PCR should reduce the disparity in data from multiple centers in future. However, a compartmental effect of monoclonal antibody-based therapy may introduce new difficulties in the interpretation of data.

**Therapy-targeting the CD20 antigen**

Rituximab, a chimeric, mouse-human antibody directed against the CD20 antigen, is approved for use in relapsed low grade lymphoma based on a response rate of 48% [26]. Among patients with follicular lymphoma, the response rate was higher, 60%. The median duration of response was 11.5 months. Additional studies demonstrated the feasibility of re-treatment: previous responders had a 43% response rate. Activity has been seen among patients who relapsed after transplantation, the elderly, chemo-resistant patients, and those with bulky tumors. A virtual exploration of clinical research activities has followed the introduction of Rituximab. Studies in untreated patients, use of different doses, schedules and duration, and combination with conventional cytotoxics are in progress. Enthusiasm for combination therapy results from the non-overlapping toxicities and different mechanisms of action. One of the earliest experience was with the combination of CHOP chemotherapy and Rituximab [27]. In this study, which included primarily untreated follicular lymphoma patients, the feasibility of the approach was demonstrated. Preliminary data appear encouraging, with a failure-free survival of 70% at four years. However, as noted above, the heterogeneity of follicular lymphoma must be considered in the interpretation of results.

Another approach has been to use the CD20 antigen as a target for the delivery of irradiation, radioimmunotherapy. I\(^{131}\) and Y\(^{90}\) are the two isotopes linked to anti-CD20 antibodies which are farthest along in their clinical development. The pivotal trial of tositumomab (I\(^{131}\)-labeled anti-B1) included heavily pre-treated patients, with more than two prior relapses. Compared to the most recent chemotherapy exposure, tositumomab ("Bexxar") yielded a significantly higher rate of response and longer response duration [28]. Additional studies with this product include a series of untreated patients in which molecular remissions were reported. Press et al. have incorporated radioimmunotherapy into the prepar-
atory regimen prior to autotransplantation for follicular lymphoma, with outstanding preliminary results [29].

Clinical development with Y\(^{90}\) chelated to the Y2B8 anti-CD20 antibody are likewise proceeding. Early data demonstrate high response rates, a favorable tumor to target ratio and the expected toxicity profile [30]. The differences in path length and other attributes of the radioisotopes suggest theoretic differences in their application according to clinical circumstances. These questions provide fertile areas for future investigation.

The application of different response criteria for the reporting of results in these studies led to controversy and confusion. Recently, an international consensus for response criteria in non-Hodgkin’s lymphoma has been published [31]. Hopefully this will resolve future differences.

**Novel therapies**

For a number of years, Levy and colleagues have investigated the idiotype, a unique surface determinant of B-cell malignancy, as a target for therapy. The observation of antigenic modulation following treatment with anti-idiotypic antibodies suggested that an active approach to immunotherapy would be more effective in follicular lymphoma. Studies with idiotype vaccines have been evolving over the last decade. Alterations in the vaccine preparation and its administration are aimed at achieving immune responses, both humoral and cellular, in every patient. An important observation of this work is the close correlation between tumor burden and detection of an immune response. Overall survival among patients treated by Levy et al. was correlated with the ability to mount an immune response [32].

Another area of active and promising investigation is **BCL-2** antisense therapy, which has completed successful phase I testing [33]. Nadler and associates are developing strategies to enhance antigen presentation by follicular lymphoma cells and boost the T-cell response. Allogenic transplantation, with its purported graft-versus-lymphoma effect, has been studied in selected patients [34]. The treatment-related mortality remains prohibitive for application of this approach early in the disease course, but modifications of allotransplantation may prove to be less toxic while maintaining efficacy.

**Conclusions**

The number of potential therapeutic options for the treatment of follicular lymphoma translate into a particularly exciting time for clinical investigation. The goal of new treatments remains permanent eradication of tumor. However, the sequential application of treatments with different mechanisms of action is another means of prolonging survival in these indolent disorders. It is essential that physicians treating patients with follicular lymphoma demonstrate restraint in the application of new treatment and cooperate in the study of new therapies in carefully designed phase II and III studies. Figure 1 shows the design of a representative trial in progress, E1496. Patients with advanced follicular lymphoma are prospectively evaluated for tumor burden and randomization to one of two chemotherapy regimens is stratified by tumor burden. A second randomization to 'maintenance' Rituximab or observation is likewise stratified on the basis of clinical features. Finally, landmark analysis of molecular remission using real-time PCR is incorporated after treatment.

We are making progress in follicular lymphoma. The plethora of candidate therapies holds the promise that the disciplined study of new agents with attention to prognostic features will provide the long-sought survival advantage.

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