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Review

Current treatment of follicular non-Hodgkin's lymphoma

M. Reiser*, V. Diehl

Klinik I für Innere Medizin, University Hospital Cologne, Joseph-Stelzmann-Str. 9, 50924 Cologne, Germany

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Abstract

56 200 new cases of NHL are expected to be diagnosed in the United States (US) per year. For reasons that are not fully understood, the number of new cases per year has nearly doubled in the past three decades. Most patients with follicular lymphoma are over 50 years of age and present with widespread disease at diagnosis. Nodal involvement is very common, often accompanied by splenic and bone marrow disease. Despite the advanced stage, the median survival ranges from 8 to 12 years. The vast majority of patients with advanced stage follicular lymphoma are not cured using the current therapeutic options. The rate of relapse is fairly consistent over time, even in patients who have achieved complete responses (CRs) to treatment. Therapeutic options in follicular NHL include watchful waiting, oral alkylating agents, purine nucleoside analogues, combination chemotherapy, interferon and monoclonal antibodies. Radiolabelled monoclonal antibodies, autologous or allogeneic bone marrow or peripheral stem cell transplantation are under current clinical evaluation. The approval of rituximab, an unconjugated chimeric antibody against the CD20 antigen for the treatment of relapsed follicular B-cell NHL marked a milestone in the development of antibody treatment. In addition, newer approaches like radioimmunoconjugates with myeloablative activity induced response rates of 80–100% in heavily pretreated patients. Various clinical trials combining monoclonal antibodies with conventional therapies are currently ongoing to determine whether these new biological agents will alter the natural history of follicular lymphoma.

Keywords: Follicular lymphoma; Treatment; Monoclonal antibodies; Transplantation; Interferon; Radioimmunoconjugates

1. Introduction

In 2001, an increasing number of 56 200 new cases of non-Hodgkin's lymphoma are estimated to occur in the United States (US) [1]. 35% of all cases with non-Hodgkin's lymphoma (NHL) in the US and approximately 22% in Europe [2,3] are classified as follicular lymphoma.

Follicular lymphoma are defined as a neoplasm of follicle centre B-cells, which have at least a partially follicular pattern. In the past, various terms have been used in the different lymphoma classifications. The recently proposed World Health Orgnanization (WHO) classification [4] uses the term follicular lymphoma synonymously for the follicle centre lymphoma, follicular of the REAL classification [5]. The low-grade lymphoma 'centroblastic-centrocytic' of the KIEL classification [6] are classified as follicular lymphoma grade 1 + 2. The high-grade lymphoma 'centroblastic', follicular is classified as follicular lymphoma grade 3. Due to its significantly different prognosis and therapy, this entity will be excluded from the following discussion.

Although epidemiological studies indicate that environmental factors like exposure to chemicals, herbicides and the use of hair dyes may play an important role in the aetiology of NHL, the aetiology of follicular lymphoma remains unclear [7].

Most patients with follicular lymphoma are over 50 years of age and present with widespread disease at diagnosis. The bone marrow is involved in 50%. Only a 1/3 of patients present with a localised stage of disease at the time of diagnosis. Early-stage (I and II according to the Ann Arbor Classification) follicular NHL can be effectively treated with radiation therapy alone curing approximately 50% of stage I and 25% of stage II patients [8] (Table 1).

Nodal involvement is very common, often accompanied by splenic and bone marrow disease. Despite the advanced stage, the median survival ranges from 8 to 12 years, leading to the designation of being 'indolent' [2].

* Corresponding author. Tel.: +49-221-478-6628; fax +49-221-478-3531.

E-mail address: marcel.reiser@uni-koeln.de (M. Reiser).

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Table 1
Indolent lymphoma—treatment strategies

Stage I/II
• Only 15–20% of patients
• Limited disease is potentially curable, treatment should not be deferred
• Radiation therapy (RT) alone as IF or EF
It remains unclear if OS is improved by additional chemotherapy
Stage (III/IV)
• Palliative treatment
• Orally chlorambucil is effective (clinical remission 65%)
• Combination chemotherapy showed higher CR rates, but did not improve survival
• Patients <60 years of age may benefit from myeloablative therapy with autologous stem cell support $\pm$TBI
• Maintenance therapy with IFN showed significantly longer DFS, but failed to improve OS

OS, overall survival; CR, complete remission; TBI, total body irradiation; IFN, interferon; DFS, disease-free survival; IF, involved field radiotherapy; EF, extended field radiotherapy.

However, the vast majority of patients with advanced stage follicular lymphoma are not cured with the current therapeutic options. The rate of relapse is fairly consistent over time, even in patients who have achieved complete responses (CRs) to treatment. Therefore, follicular lymphomas are characterised by a continuous pattern of relapse and relatively long median survivals. The heterogeneity in these diseases has led to various options for treatment including watchful waiting, oral alkylating agents, purine nucleoside analogues, combination chemotherapy, interferon and monoclonal antibodies. Radiolabelled monoclonal antibodies, autologous or allogeneic bone marrow or peripheral stem cell transplantation are under current clinical evaluation [9].

Rearrangements of *bcl-2* are present in over 90% of patients with follicular lymphoma; overexpression of the bcl-2 protein is associated with the inability to eradicate the lymphoma through the inhibition of apoptosis [10]. Patients achieving a molecular response, as defined by a polymerase chain reaction (PCR)-negative status during the first year of therapy showed a significant better failure-free survival (FFS). No significant difference has been observed so far in terms of survival [11].

2. Deferred therapy

In selected patients with advanced stage follicular lymphoma, cytotoxic therapy may be deferred until disease progression (watchful waiting) without any significant influence on overall survival [12]. Several authors compared an initial no-treatment policy versus combined modality treatment without any differences being observed in the overall survival. Brice and colleagues, for example, performed a randomised study in patients with follicular lymphoma and a low tumour burden. No difference in the overall survival rates at 5 years was observed when patients were treated with prednimustine, interferon-alpha or a delay of any treatment until clinically meaningful progression [13]. In a group of 83 patients with advanced disease, who were initially managed without therapy, 10-year overall survival was 73%, with spontaneous regressions occurring in 23% [14]. Therefore, it is generally accepted that, in advanced stage patients with a modest tumour burden, treatment can be delayed until disease progression.

3. Conventional chemotherapy

One of the first effective treatment options for patients with advanced stage follicular lymphoma was the combination of chlorambucil and prednisone [15]. The combination is well tolerated and effective in up to 65% of the patients [16]. With the addition of vincristine (COP) [17], 5-year overall survival rates of 60% have been achieved [18]. Due to improved treatment outcomes in aggressive lymphoma with the addition of the anthracycline doxorubicin in the CHOP regimen [19], the combination has also been widely used in follicular lymphoma. Various other treatment regimens including additional drugs like procarbacine, bleomycin, methotrexate, cytarabine and etoposide have also been evaluated without any significant improvement in overall survival. Therefore, the intensification of conventional chemotherapy regimens has improved response rates in patients with advanced stage follicular lymphoma without improving overall survival [12].

4. Purine nucleoside analogues

Fludarabine and 2-chlorodeoxyadenosine (cladribine) are two relatively new drugs which have been evaluated in numerous clinical trials in the past years [20–23]. Both drugs are highly effective and induce remission rates between 70 and 80% in previously untreated patients with advanced stage follicular lymphoma. As second-line treatment in patients with relapsed or

refractory disease, the use of the two drugs results in response rates of 50% [24–26]. In a randomised trial, the two drugs appear to be cross-resistant. While showing similar response rates and durations, more patients experienced persistent haematological toxicity in the 2-chlorodeoxyadenosine group [27].

Several authors reported clinical trials with combination regimens combining purine analogues with anthracyclines like mitoxantrone and idarubicin or alkylating drugs like cyclophosphamide. Although these combination chemotherapy regimens seem to improve event-free survival, there is no evidence that overall survival is improved significantly [12,28,29].

A third purine nucleoside analogue is pentostatin. The literature indicates that the drug is less active in follicular lymphoma compared with fludarabine and 2-chlorodeoxyadenosine. However, many studies investigating pentostatin in follicular lymphoma have evaluated a large number of patients previously treated with the other purine analogues. As these agents are most likely cross-resistant, it is difficult to compare the response rates [30].

5. Interferon

Recombinant human interferon-alpha has demonstrated significant activity against follicular lymphoma. Against this background, interferon-alpha was incorporated into the first-line treatment of follicular lymphoma either as simultaneous treatment with initial cytotoxic chemotherapy or as maintenance treatment after successful initial chemotherapy. Of the five prospective randomised trials comparing interferon-alpha in combination with initial chemotherapy (single alkylating agent) versus chemotherapy alone, three studies showed no beneficial effect of interferon-alpha. In contrast, a significant improvement in the remission rate and remission duration was observed in two studies when interferon-alpha was combined with anthracycline-containing regimens. Five prospective randomised studies evaluated the role of interferon-alpha as maintenance therapy after successful cytoreductive chemotherapy. Four of these studies have found a significant improvement in disease-free survival only in patients achieving a CR with the initial cytoreductive treatment [31].

In a study of the German Low Grade Lymphoma Study Group, low-grade lymphoma patients received high doses of interferon-alpha with no restriction on the duration of therapy. At 4 years, 45% of patients receiving interferon-alpha maintenance therapy remained relapse-free, compared with 26% of patients in the untreated control group ($P = 0.003$) [32]. The study group is currently comparing high-dose chemotherapy versus interferon maintenance in patients with follicular NHL who are aged < 60 years.

6. High-dose chemotherapy with stem cell support

In order to overcome the drug resistance of malignant cell clones, effective drugs are escalated in maximum tolerated doses with autologous stem cell support. Long-term follow-up on high-dose therapy suggests a potential role for this modality in patients with follicular lymphoma. Horning and colleagues recently reported with a median follow-up of 6.5 years an estimated 10-year survival rate after transplantation of 86% [33]. Several studies reinforce past findings that patients with chemosensitive relapse are good candidates for high-dose therapy. In our own patients, overall survival and freedom from treatment failure for 32 patients with primary refractory or relapsed indolent lymphoma treated with the Dexa-BEAM (dexamethasone, carmustine [BCNU], etoposide, cytarabine and melphalan) regimen was 68 and 65% at 2 years, respectively. [34]. Compared with historical controls high-dose chemotherapy improves event-free and overall survival [35]. However, with high-dose chemotherapy, a prolonged freedom from relapse can be achieved in patients with follicular lymphoma but, as yet, there is no survival advantage compared with conventional treatment [36]. Randomised trials with longer follow-up periods are necessary to answer the question of whether high-dose chemotherapy has an impact on survival.

7. Allogeneic bone marrow transplantation

Due to a high transplantation-related mortality rate of 30%, only a limited number of patients with follicular lymphoma have received allogeneic bone marrow transplantation. In addition, the majority of patients have received an autologous transplantation in the earlier course of disease. In an observational study of 113 patients receiving HLA-identical sibling bone marrow transplants conducted at 50 centres participating in the International Bone Marrow Transplant Registry (IBMTR), the 3-year overall survival rate was 49%, with a probability of recurrence of 16% [37]. Therefore, allogeneic bone marrow transplantation may be a therapeutic option for a certain subset of patients who are refractory to standard treatment.

8. Monoclonal antibody treatment

Significant advances have been made in the application of monoclonal antibody-based therapies to the treatment of patients with indolent NHL. The most promising areas appear to be the use of unconjugated monoclonal antibodies and the use of radiolabelled monoclonal antibodies. The approval by the US Food and Drug Administration (FDA) of rituximab (rituxan),

an unconjugated chimeric antibody against the CD20 antigen for the treatment of relapsed low-grade or follicular B-cell NHL marked a milestone in the development of these antibody-based treatments [38]. In the pivotal trial of the anti-CD20 antibody, rituximab, patients with relapsed low-grade or follicular lymphoma received rituximab 375 mg/m^2 intravenously (i.v.) weekly for four doses. 166 patients were entered and in an intent-to-treat group, 48% responded. With a median follow-up of 11.8 months, the projected median time to progression for responders is 13.0 months. The response rate of 48% with rituximab was comparable to results with single-agent cytotoxic chemotherapy. Toxicity was mild [39].

Czuczman and colleagues reported the first successful clinical trial combining rituximab with standard-dose combination chemotherapy CHOP in the treatment of patients with indolent B-cell lymphoma. 100% of the treated patients responded to the combination, and 58% of them achieved a CR. At the time of publication, with a median follow-up of 2.5 years, 74% of the patients were continuing in response [40]. These results have been updated with a follow-up now reaching 5 years and more than 60% of the patients have remained in CR.

Preliminary results of other types of combinations with fludarabine, DHAP (dexamethasone, cytosine arabinoside, cisplatin), CVP (cyclophosphamide, vincristine, prednisone) and FCM (fludarabine, cyclophosphamide, mitoxantrone) in chemotherapy-naïve or pre-treated patients have been reported. All reports demonstrated high response rates (often better than in other studies with the same regimen, but without rituximab) and the absence of additive toxicity. However, the only conclusions that may be drawn from these studies are (a) rituximab combined with chemotherapy did not add toxicity to the chemotherapy; and (b) the response rate seemed higher than with chemotherapy alone and the duration of response seemed longer. Therefore, ongoing randomised trials have to prove the benefit of adding rituximab to the chemotherapy regimens.

To enhance the therapeutic potency of monoclonal antibodies, investigators have conjugated them to cytotoxic radioisotopes to target the radiotherapy specifically to the tumour sites and improve the overall and complete remission rates. Most commonly, iodine 131 ([I^{131}]) and yttrium ([Y^{90}]) are linked to anti-CD20 antibodies. Both tositumomab (Bexxar®) and ibritumomab (Zevalin®) affect tumour cells by emission of beta particles. The beta particles of [Y^{90}] are more energetic than those of [I^{131}]. In addition, [I^{131}] emits long-range gamma rays presenting a potential radiation hazard for other persons making a hospitalisation for radiation isolation necessary [41].

Kaminski and colleagues have published an updated single institution experience with the [I^{131}]-tositumomab antibody. 35 (83%) of 42 patients with relapsed or refractory low-grade NHL responded to single treatment with a median progression-free survival of 12 months [42].

Witzig and colleagues reported the first randomised trial comparing radioimmunotherapy ([Y^{90}]-ibritumomab) to unconjugated monoclonal antibody therapy (rituximab) with a higher complete response rate of 30% versus 16% in the radiolabelled antibody group. Both regimens were well tolerated, but significantly more myelosuppression occurred in the radiolabelled antibody group [43].

In addition, radioimmunoconjugates with myeloablative activity induced response rates of 80–100% in heavily pretreated follicular lymphoma patients [44].

Therefore, radiolabelled antibodies can produce substantially higher overall and complete response rates than corresponding unlabelled antibodies, but to date advantages in overall and progression-free survival have not yet been demonstrated.

Various clinical trials combining radiolabelled and unlabelled antibodies with conventional therapies are currently ongoing to determine whether these new biological agents will alter the natural history of this disease in follicular lymphoma patients.

9. Conclusions

In follicular lymphoma, survival data have not improved over the last three decades, leaving the vast majority of patients with no chance of cure. For advanced stage disease, current treatment options include deferred therapy, oral alkylating agents, purine nucleoside analogues, combination chemotherapy, interferon and monoclonal antibodies. Radiolabelled monoclonal antibodies, high-dose chemotherapy with stem cell support and allogeneic bone marrow transplantation are under clinical evaluation. Significant progress has been made with the introduction of monoclonal antibody-based therapy, but further studies have to prove if these new treatment options will alter the natural history of the disease. Therefore, clinicians treating patients with follicular lymphoma should enter patients in the ongoing phase III trials in order to define the role of these new treatment options in follicular lymphoma.

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