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Advances in the management of follicular lymphoma

Michele Ghielmini

Oncology Institute of Southern Switzerland, Oncologia medica, Bellinzona, Switzerland

Corresponding author:
Michele Ghielmini
Email: mghielmini@ticino.com

A B S T R A C T

In adults, follicular lymphoma (FL), characterized by a long clinical course with frequent relapses, accounts for up to one-third of cases of non-Hodgkin's lymphoma. With the advent of newer treatment modalities therapeutic goals are shifting from improving quality of life to prolonging survival. Prognostic factors can help to determine the most effective treatment approach: *aggressive* treatment which may provide longer remission or *softe*r treatment options that offer a more favorable tolerability profile. Chemotherapeutic regimens supplemented with additional treatment modalities, such as interferon therapy, appear to offer improved clinical and survival outcomes compared with chemotherapy alone. Chemotherapy followed by allogeneic bone marrow transplantation is associated with more favorable outcomes than autologous stem-cell transplantation but at the expense of higher treatment-related mortality rates. Immunotherapy, in the form of radiolabelled/nonradiolabelled monoclonal antibodies has provided new hope for the treatment of patients with FL. The addition of rituximab to chemotherapy has been shown to prolong time to treatment failure and time to progression as well as improving survival. Radioimmunotherapy with yttrium-90 (^{90}Y)-ibritumomab tiuxetan and rituximab improves response rates in patients with relapsed or refractory FL without an increased risk of secondary malignancies. Data on the use of radioimmunotherapy strategies suggest that their use in combination with other treatment modalities can have a higher lymphoma-killing capacity. Whether or not this approach will translate into longer patient survival or a cure for a proportion of patients remains to be determined from ongoing randomized clinical trials.

Introduction

Follicular lymphoma (FL) is the most common non-Hodgkin's lymphoma (NHL), and accounts for up to one-third of NHL cases in adults.[1] In most patients, FL is characterised by a long clinical course with frequent relapses that vary in clinical aggressiveness over time.[2] The early initiating event in FL is thought to be translocation of t(14;18)(q32;q21) with downstream bcl-2 overexpression.[3] The majority of the observed t(14;18)(q32;q21) translocations are characterised by 1 of 2 common breakpoints: the major breakpoint region (MBR) and the minor cluster region (mcr).3 FL develops from germinal centre cells following this translocation and subsequent genomic alterations which lead to the disease

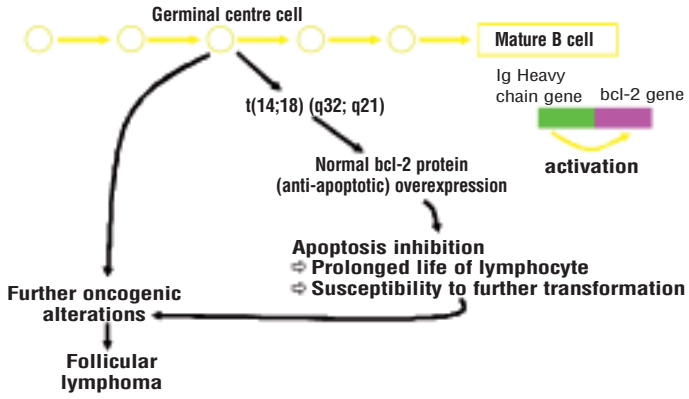

Figure 1: Pathogenesis of follicular lymphoma according to the two pathways hypothesis.

(Figure 1). There is also a hypothesis that these latter alterations could appear without previous t(14;18) translocation.

There is a significant disparity in bcl-2 frequency between Western and Asian FL patient populations. This suggests FL may be a heterogeneous malignancy encompassing entities with distinct molecular pathogenesis and potentially distinct clinical manifestations.3

Factors affecting treatment choice for follicular lymphoma

The decision to choose either a conservative *(soft)* or pseudo-curative *(aggressive)* treatment approach can be aided by the use of prognostic factors. The morphologic subclassification of FL has been used to guide the choice of therapy in patients with FL. According to the World Health Organization (WHO) classification, FL is graded as 1, 2, 3a and 3b according to the number of large transformed cells (centroblasts) per high-power field.[4] However, although these criteria appear objective, grading has a notoriously poor reproducibility due to the subjective nature of morphologic grading and the inherent inadequacy of the criteria set for *transformed cells*.[2]

As the prognosis of FL is heterogeneous, the validated Follicular Lymphoma International Prognostic Index (FLIPI) score supports patient evaluation and treatment choice.1 The FLIPI also appears to be more discriminant than the International Prognostic Index (IPI) proposed for aggressive NHL. The IPI was not designed to investigate predictive factors and therefore cannot identify patients in whom intensive therapy has to be tested. Three risk groups have been defined using FLIPI: low risk (0–1 adverse factors), intermediate risk (2 adverse factors) and high risk (≥3 adverse factors). The overall survival of patients at high-risk is lower than those patients with a low or intermediate risk (Figure 2).[1] It is important to note that since the majority of patients (≈70%) can be classified as low or intermediate risk, the discriminative value of FLIPI is somewhat limited. Furthermore, this index has only been formally validated for its prognostic value at diagnosis, and therefore other means of stratification would be valuable in guiding the choice of therapy.[2]

The selection of aggressive treatment for FL based on histologic grading and clinical criteria remains suboptimal, and in up to 30% of all cases these methods prove to be inconclusive.[2] However, a gene expression profile of 81 genes has been developed that can distinguish low-grade from high-grade disease (with an accuracy of 93%) even when histologic grading is ambiguous.[2] This FL stratifi-

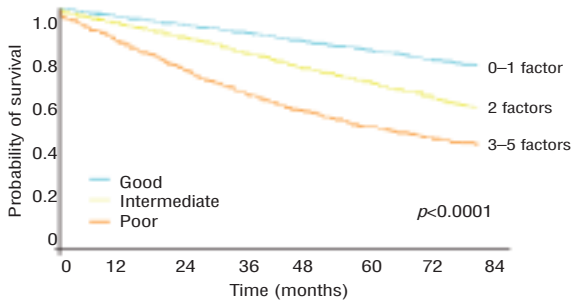

Figure 2: Overall survival of patients (n=919) used for validation of the Follicular Lymphoma International Prognostic Index (FLIPI). Blue line indicates patients in the low-risk group (0–1 factor); yellow line, patients in the intermediate-risk group (2 factors); orange line, patients in the high-risk group (≥3 factors) (Solal-Celigny *et al.*, 2004). Reproduced with permission from Solal-Celigny P, et al. Follicular lymphoma international prognostic index. *Blood 2004;104:1258-65.*

cation profile appears to be a more reliable marker of clinical behavior than current methods, and may be useful in guiding clinical decision making both at presentation and diagnosis.

Quantitative PCR of bone marrow bcl-2/IgH+ cells at diagnosis can predict treatment response and long-term outcome in FL, and may therefore influence choice of therapy.[5] A low level of bcl-2/IgH+ cells at diagnosis was the best predictor for a complete clinical and molecular response. The 5-year event-free survival rates for patients with low/intermediate versus high bcl-2/IgH+ cell levels was 59 and 32%, respectively (p=0.02). In addition, Farinha et al. have suggested that the lymphoma-associated macrophage content is an independent predictor of overall survival in FL.[6]

Treatment of follicular lymphoma

The primary treatment goal in relapsed FL has traditionally been the improvement of patient quality of life. However, with the advent of new treatment modalities, prolonging survival is potentially becoming a more realistic goal. The balance of treatment lies between *aggressive* treatment which may provide longer remission and *softer* treatment options which tend to have a more favorable tolerability/adverse event profile.

As the evolution of FL is usually very indolent (median survival of 9 to 10 years), long-term survival is common, irrespective of the treatment received. For example, approximately 20% of patients with advanced but untreated FL remain alive and well 15 years after diagnosis. In addition, approximately 20% of patients treated with single agent alkylators (e.g. chlorambucil or cyclophosphamide) remain alive and in first remission 15 years from diagnosis.[7] Since, neither chemotherapy with a single-alkylating agent nor aggressive combination chemotherapy cure advanced low-grade NHL, even when combined with radiotherapy, the *watch and wait* approach remains a viable treatment option.[7] Evidence suggests that an initial policy of watchful waiting in patients with asymptomatic, advanced stage low-grade NHL is appropriate, especially in patients older than 70 years.[7]

Although FL remains incurable, evolving therapies such as the incorporation of biologic agents, has led to a significant improvement in treatment outcomes for patients with advanced FL. Liu et al. analysed five sequential cohorts of patients with stage IV indolent FL (n=705; treated between 1977 and 2002) and reported improvements in 5-year overall survival from 64 to 90%.[8] Across this time period, a stepwise improvement was apparent with the addition of each new treatment regimen (e.g. CHOP-B: cyclophosphamide, doxorubicin, vincristine, prednisone, and bleomycin, FND: fludarabine, mitoxantrone and dexamethasone, interferon), particularly with the addition of rituximab to chemotherapy.[8]

Combination chemotherapy

Prolonged remission of FL does not necessarily mean longer patient survival (Peterson et al., 2003). The Cancer and Leukemia Group B (CALGB) compared single agent (cyclophosphamide) with combination chemotherapy (CHOP-B) in patients with stage III or IV FL, with treatment continued in responders for 2 years beyond maximal response.[9] At 10 years, there was a nonsignificant trend towards a greater proportion of patients that were failure-free (25 *vs*. 33%) with the CHOP-B regimen, although survival rates were similar for the two treatment arms (44 *vs*. 46%). However, an unplanned subanalysis demonstrated that combination chemotherapy was associated with significantly better failure-free (p=0.005) and overall survival (p=0.024) in patients with follicular, mixed small cleaved cell lymphoma (FML). The investigators concluded that while, in general, there was no advantage with the initial use of a relatively intensive treatment combination patients with FML experienced improved survival.

Interferon plus chemotherapy

Evidence indicates that the addition of interferon (IFN)-α2 to a chemotherapeutic regimen appears to prolong survival in patients with FL. A meta-analysis of ten phase III studies, involving 1,922 newly diagnosed patients with FL, indicated that the addition of IFN-α2 to initial chemotherapy did not significantly influence response rate, but duration of remission (p=0.000001) and overall survival (p=0.004) were significantly improved.[10] The survival advantage favoring IFN-α2 was observed when IFN-α2 was administered at any time point in patients receiving intensive initial chemotherapy (p=0.00005), at a dose of ≥5 million units (p=0.000002), at a cumulative dose of ≥36 million units per month (p=0.000008), and with initial chemotherapy rather than as maintenance therapy (p=0.004). The results of this meta-analysis support the incorporation of IFN-α2 into a treatment regimen for patients with FL.

Autologous and allogeneic stem-cell transplantation

The potential impact of high-dose chemotherapy plus autologous stem cell transplantation (ASCT) on survival outcomes remains controversial. The efficacy of high-dose chemotherapy followed by ASCT in first-line FL has been assessed in patients aged <60 years old with a high tumor burden. Patients treated with high-dose therapy and stem cell support had a higher response rate (69 *vs*. 81%, p=0.045) and a longer median event-free survival at 5 years (not reached *vs*. 45 months) compared with doxorubicin-based chemotherapy plus interferon.[11] However, this did not translate into a better survival rate due to an excess of secondary malignancies following transplantation. Data from a recently published study comparing similar treatment regimens support these findings; after a median of 7.5 years there were no differences between standard chemotherapy plus interferon and a CHOP regimen followed by ASCT in terms of event-free and overall survival.[12] These studies suggest that ASCT should not be considered as standard first-line treatment for FL patients who are <60 years old with a high tumor burden but should be reserved for relapsing patients.

The use of high-dose chemotherapy followed by ASCT has been shown to prolong overall (p=0.026) and progression-free sur-

vival (p=0.0009) in relapsed FL patients.[13] This study also determined the additional value of B-cell purging of the stem-cell graft. The overall survival rates at 4 years were 46, 71 and 77% for chemotherapy, chemotherapy followed by unpurged ASCT and chemotherapy followed by purged ASCT, respectively. There appeared to be no therapeutic benefits associated with purging of the stem-cell graft in terms of patient outcomes.

In 904 patients with FL, 5-year recurrence rates for allogeneic SCT, purged and unpurged ASCT were 21, 43 and 58%, respectively.[14] However, higher 5-year treatment-related mortality rates were observed with allogeneic SCT (30, 14 and 8%, respectively; p<0.001). Similar outcomes were reported when high-dose chemotherapy was followed by allogeneic SCT for refractory or recurrent indolent NHL; there was a reduced probability of disease progression (19 *vs*. 74%; p=0.003) but higher treatment-related mortality rates compared with ASCT.[15]

In patients with NHL, standard therapies have been associated with an increased risk of developing treatment-related myelodysplastic syndrome (MDS) or acute myelogenous leukemia (AML).[16] Evidence suggests that up to 10% of NHL patients treated with either conventional-dose chemotherapy or high-dose therapy and ASCT may develop MDS or AML within 10 years of primary therapy. However, limiting exposure to alkylating agents and eliminating total-body irradiation from transplantation conditioning regimens may reduce this risk.[16]

Allogeneic bone marrow transplantation

Allogeneic bone marrow transplantation (BMT) has also been assessed in patients with recurrent low-grade lymphoma.[17] Data from a small study (n=10), including 7 patients with FL, demonstrated that 80% of patients treated with myeloablative therapy and allogeneic BMT achieved complete remission and this response compared favorably with autologous BMT.[17] However, the weight of evidence suggests that allogeneic BMT is associated with more favorable outcomes than autologous BMT. Patients with poor-prognosis low-grade lymphoma (n=28), including 24 patients with FL, had a lower probability of relapse or disease progression (0 *vs*. 83%; p=0.002) and higher progression-free survival rates (68 *vs*. 22%; p=0.049) with allogeneic versus autologous BMT.[18]

Monoclonal antibody therapy

Immunotherapy, either in the form of allogeneic transplantation or radiolabelled/non-radiolabelled monoclonal antibodies has provided new hope for the treatment of patients with FL. Rituximab, a chimeric monoclonal antibody directed against the B-cell CD20 antigen, has been utilised for the therapy of NHL. Data from the systemic treatment of advanced FL indicate that improved clinical and survival outcomes can be achieved with rituximab plus chemotherapy.[19-21] Herold et al. reported that the addition of rituximab to mitoxantrone, chlorambucil, and prednisolone (MCP) chemotherapy significantly improves the outcome of treatment naïve patients with advanced indolent NHL compared with MCP alone.[19] Overall response rates (92.4 *vs*. 75%), complete response rates (49.5 *vs*. 25%), and 2-year event-free survival rates (83 *vs*. 43%) were significantly higher with MCP plus rituximab (p<0.0001). In patients with advanced-stage FL, the addition of rituximab to a CHOP regimen also significantly prolonged remission (p=0.001) and improved survival (p=0.016) compared with CHOP alone.[20] Similarly, the addition of rituximab to

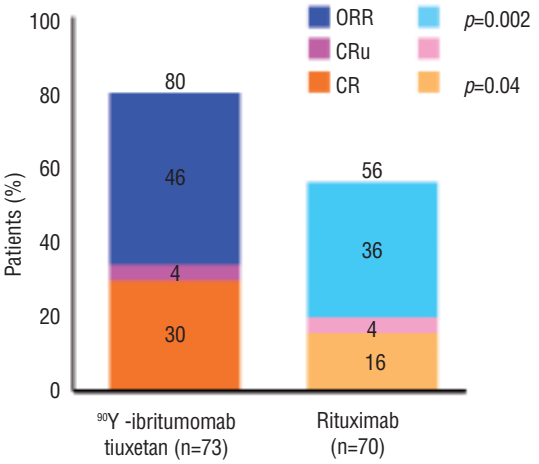

Figure 3: Treatment response rates (LEXCOR assessed response) at 12 months in FL patients treated with either ^{90}Y-ibritumomab tiuxetan or rituximab. CR, complete response; CRu, complete response unconfirmed *(Witzig et al., 2002)*.

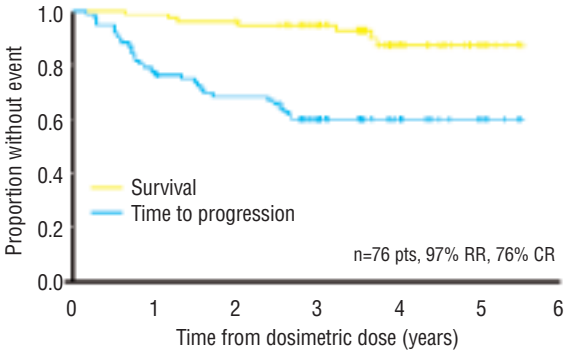

Figure 4: Survival and time-to-progression for all patients. The data are for all 76 patients treated with ^{131}I-tositumomab therapy as initial therapy for advanced stage, follicular, low-grade, B-cell NHL (*Kaminski et al, 2005*). *Reproduced with permission from Kaminski MS, et al. ^{131}I-tositumomab therapy as initial treatment for follicular lymphoma. N Engl J Med 2005;352:441–9. ©2005 Massachusetts Medical Society. All rights reserved.*

cyclophosphamide, vincristine and prednisone (CVP) has also prolonged time to treatment failure (median 27 *vs*. 7 months; $p<0.0001$) and time to progression (median 32 *vs*. 15 months; $p<0.0001$) relative to CVP alone in patients with advanced untreated FL.[21]

Treatment schedules with rituximab in patients with FL have produced varying response rates from 52 to 62% with response durations ranging from 13 to 31 months.[22–26] After a median follow-up of 41 months, maintenance rituximab therapy (standard 4-week courses administered at 6-month intervals) demonstrated higher overall and complete response rates compared with a standard 4-week course.[26] In addition, prolonged rituximab administration (375 mg/m^2 every 2 months x 4) following standard treatment (rituximab 375 mg/m^2 weekly x 4) significantly improved event-free survival (23 *vs*. 12 months; $p=0.02$) at a median of 35 months compared with standard treatment. This difference in response was particularly notable in chemotherapy-naive patients (36 *vs*. 19 months; $p=0.009$).[25]

Irradiation as a treatment option in FL

Murtha et al. have reported that patients with stage III FL treated with primary radiotherapy (total lymphoid irradiation or whole body irradiation) can achieve median overall survival, cause-specific survival, freedom from relapse, and event-free survival of 9.5, 18.9, 7.1 and 5.1 years, respectively.[27] Of particular note, overall survival was most strongly and independently predicted by patient age ($p=0.05$). The important difference between cause-specific survival and event-free survival, and the lack of a plateau in the survival curve, are due to the long-term side-effects of radiotherapy given at such a high total dose (40 to 48 Gy). However, these data appear comparable with those achieved using other therapeutic approaches.

The use of low-dose (4 Gy) involved field radiotherapy in patients with recurrent indolent lymphoma was associated with overall response and complete response rates of 92 and 61%.[28] This therapeutic approach is not

associated with significant long-term toxicity and should be considered in patients with recurrent disease.

Radioimmunotherapy combines biologic and radiolytic mechanisms to target and destroy tumour cells, thus offering a needed therapeutic alternative for patients with refractory NHL, including those with FL. A phase III randomised study has compared yttrium-90 (^{90}Y)-ibritumomab tiuxetan with rituximab in patients with relapsed or refractory low-grade, follicular, or transformed CD20$^+$ NHL.[29] Data confirm that ^{90}Y-ibritumomab tiuxetan produced clinically significant higher overall response rates (p=0.002) and complete responses (p=0.04) compared with rituximab alone (Figure 3). A single one-week course of ^{131}I-tositumomab therapy as initial treatment in patients with advanced FL produced a complete response in 75% of treated patients and a median progression-free survival of 6.1 years (Figure 4).[30]

Two frequent concerns regarding the use of radioimmunotherapy are that it may cause AML and/or MDS (as seen with standard therapies), and that it might not allow subsequent treatment. However the use of ^{90}Y-ibritumomab tiuxetan does not increase the risk of developing these secondary malignancies,[31] or preclude subsequent therapy upon relapse.[31-33] Similar results have been reported with ^{131}I-tositumomab.[34,35]

From a treatment cost perspective, a cost-effectiveness analysis has suggested that for each third-line treatment for relapsed FL, where ^{90}Y-ibritumomab tiuxetan is used rather than a 4-dose regimen of rituximab 375 mg/m^2, the additional cost to the payer (average EUR 6,835) provides a benefit to the patient of an average of 8.2 additional disease-free months, over and above what would have been gained with 4-dose rituximab therapy.[36] Furthermore, when the costs and benefits of ^{90}Y-ibritumomab tiuxetan are compared with an 8-dose rituximab regimen, ^{90}Y-ibritumomab tiuxetan appears to be the more cost-effective strategy.

Conclusions

Given the long clinical course of FL, the benefits of inducing longer remission via the use of aggressive treatment strategies must be weighed against any potential tolerability issues. The addition of allogeneic BMT to a chemotherapeutic regimen appears to improve clinical outcomes compared with the use of ASCT but at the expense of greater treatment-related mortality. Evidence suggests that the incorporation of biologic agents into chemotherapeutic regimens improves clinical and survival outcomes, particularly in treatment naïve patients with advanced NHL. Data on the use of radioimmunotherapy strategies suggest that their use in combination with other treatment modalities can have a higher lymphoma-killing capacity. Whether or not this approach will translate into longer patient survival or a cure for a proportion of patients remains to be determined from ongoing randomized clinical trials.

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