Follicular lymphoma: managing an indolent malignancy

Follicular lymphoma is by far the most common indolent non-Hodgkin lymphoma worldwide. Management is complicated by difficulty in accurately predicting individual outcomes and judging whether, when and how best to intervene. This article illustrates key issues in the management of this fascinating and enigmatic disease.

Follicular lymphoma is a malignancy of B-lymphocytes (germinal centre B-cells) that accumulate to varying extents in the lymphoreticular, haemopoietic and extranodal compartments. Affected lymph nodes contain a mixture of small regular lymphoid cells (centrocytes) and larger more irregular lymphoid cells (centroblasts), within a variably conserved lymph node follicular architecture. Follicular lymphoma is graded from I to III depending on the number of large cells (centroblasts) seen per high power light microscope field. Grade IIIb follicular lymphoma shows effacement of the regular follicular architecture by sheets of centroblasts, and owing to its far more aggressive clinical behaviour, is neither included in the vast majority of clinical trials in follicular lymphoma, nor will it be considered further in this article. This article will discuss an illustrative case history which highlights key issues in the management of follicular lymphoma.

Diagnosis and staging

Establishing the diagnosis of follicular lymphoma currently requires observation of affected lymph node architecture, and as such, excision lymph node biopsy is the standard of care, with fine needle aspiration cytology being unhelpful.

Malignant B-lymphocytes of follicular lymphoma express characteristic cell surface markers, demonstrable by immunophenotyping; the pan-B-cell markers CD19, CD20, CD22, as well as monoclonal light chains, CD10 (in 60%), but not CD5. The chromosomal translocation (14;18) is identified in 90% of cases of follicular lymphoma, and causes rearrangement and over-expression of the anti-apoptotic protein BCL2. This protein can be readily identified in histological sections, and is thought to contribute to the pathophysiology of the accumulating malignant clone.

Follicular lymphoma is staged using the Ann Arbor system, and the majority of cases present with disease above and below the diaphragm (stage 3) or with bone marrow or extra-nodal involvement (stage 4). Half of patients have morphologically identifiable bone marrow involvement at diagnosis. Localized disease (stage 1 or 2) is rare, and will not be considered further in this article, but can be cured with radiotherapy (Vaughan Hudson et al, 1994; MacManus and Hoppe, 1996; Wilder et al, 2001).

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Case study

A 54-year-old woman presented to her GP with painless lumps in her right groin. Excision biopsy revealed grade I follicular lymphoma. Haemato-oncology review established that she had no systemic symptoms attributable to follicular lymphoma and was not troubled by the remaining small lumps in her right groin. Staging computed tomography scans revealed enlarged lymph nodes in the groin, pelvis and abdomen with a maximum diameter of 2 cm. A full blood count was normal despite low levels of follicular lymphoma demonstrated in the bone marrow trephine biopsy. Renal, liver and bone biochemistry were normal.

Incidence and prognosis

With an annual incidence of about three new cases per 100 000 of the English population, follicular lymphoma comprises 2% of all malignancies diagnosed in the UK each year. The median age at diagnosis is 60 years, with an equal sex distribution.

The worldwide incidence of all types of non-Hodgkin lymphoma, including follicular lymphoma, has been increasing at a rate of between 1 and 4% each year since the 1970s, resulting in almost a doubling in overall incidence in this time. Such analyses have also confirmed a striking geographical variation in follicular lymphoma, being more common in western nations (Muller et al, 2005). The incidence of follicular lymphoma is particularly low in China and Japan. In America, the incidence is 2–3 times higher in caucasians than in African Americans, suggesting that biological race may be a significant factor, in addition to environmental modifiers which remain unidentified.

A median survival of about 10 years from diagnosis (Horning and Rosenberg, 1984) appears to be improving to 12–14 years with modern approaches (Hoppe et

al, 1981; Fisher et al, 2005). However, the clinical course of follicular lymphoma is highly variable between individuals, and some may never require treatment even after 20 years.

Follicular lymphoma typically behaves in a variably indolent fashion, with months or years of clinically imperceptible change or very gradual asymptomatic progression interrupted by episodes of obvious clinical progression.

The Follicular Lymphoma International Prognostic Index (FLIPI) is a five factor index based on clinical characteristics at diagnosis, which was established by retrospective analysis of 4167 patients diagnosed between 1985 and 1992 (Solal-Celigny et al, 2004). Age, stage, number of nodal sites, haemoglobin concentration, and serum lactate dehydrogenase define three prognostic groups (*Table 1*). In patients with a good prognosis (0–1 adverse factors), the 10-year overall survival is 71%, falling to 36% with three or more adverse factors (*Table 2*). This may have benefit in communicating risk to patients, and in comparing populations in clinical trials and laboratory analyses of patient samples. Although prognostically useful, so far the clinical impact of the FLIPI score has been limited in determining optimal therapy for each patient group.

Case study

The patient was asymptomatic with a FLIPI score of 1. Management options were discussed. She elected to enrol into a clinical trial comparing observant management with chemoimmunotherapy incorporating the anti-CD20 antibody rituximab.

Table 1. Follicular Lymphoma International Prognostic Index (FLIPI)

Variable	Adverse factor
Age	> 60 years
Stage	> 2
Affected nodal sites	> 4
Lactate dehydrogenase	> Upper limit of normal
Haemoglobin	< 12 mg/dl

From Solal-Celigny et al (2004)

Table 2. Follicular Lymphoma International Prognostic Index (FLIPI) score and impact on survival

Prognosis	No. of adverse factors	10-year survival (%)
Good	0 or 1	71
Intermediate	2	51
Poor	3 or more	36

Following diagnosis, asymptomatic cases are sometimes observed to spontaneously regress (Gattiker et al, 1980; Krikorian et al, 1980; Horning and Rosenberg, 1984; Kumar et al, 2004), but sustained spontaneous remissions are extremely rare, and the majority eventually develop progressive lymphadenopathy and require treatment.

Treatment

Until the introduction of combined chemoimmunotherapy incorporating the monoclonal CD-20 antibody rituximab, evidence suggested that medical intervention had no significant impact on overall survival in follicular lymphoma (Hoppe et al, 1981; Young et al, 1988; Brice et al, 1997; Ardeshna et al, 2003). Chemotherapy has traditionally been reserved for symptomatic or bulky disease to induce regression to a once-more asymptomatic stage. The goal of therapy has been to maintain the best quality of life and treat only when patients develop symptoms. Any alteration to this approach requires demonstration of improved survival with early therapy, or identification of criteria that define patients at sufficiently high risk to merit early therapy (Gribben, 2007). The advent of rituximab challenges this approach. Rituximab is a chimeric (mouse/human) genetically engineered monoclonal antibody. It targets the CD-20 surface marker of mature B-cell lymphocytes. This marker is expressed on almost all B-cell lymphomas.

The aim of current management is to achieve the best possible remission for the longest period, and to prolong survival. First-line treatment options for stage 3 or 4 follicular lymphoma include single-agent or combination chemotherapy regimens based on alkylating agents, with or without steroids. Rituximab in combination with cyclophosphamide, vincristine and prednisolone (R-CVP) is a popular first-line treatment option in the UK. There is no consensus as to the best timing or combination of therapy in follicular lymphoma, and patients should always be considered for entry into clinical trials.

Case study

The patient was allocated to the observation arm of the trial, and remained symptom free for 18 months, before presenting with a swollen right leg and gradually worsening backache. Repeat biopsy showed grade I follicular lymphoma. Computed tomography scanning revealed progressive enlargement of all lymph node groups, and obstruction to venous return from the right leg, without evidence of deep vein thrombosis. A full blood count demonstrated mild anaemia and thrombocytopenia. Combination chemoimmunotherapy (rituximab-chlorambucil) was delivered as an outpatient. This produced an obvious early clinical response. Computed tomography scans and bone marrow trephine biopsy on completion of therapy

revealed a complete response with no evidence of residual enlarged nodes or bone marrow infiltration. A maintenance schedule of rituximab monotherapy every 3 months was instituted.

While eventual clinical progression is almost inevitable, good practice dictates that a repeat lymph node biopsy is taken to establish any change in grade or transformation to diffuse large B-cell lymphoma. In particular, it is important to biopsy any nodal mass that is rapidly enlarging, as transformation may occur in only one, not all nodes at the same time. Around 2% of patients with follicular lymphoma each year experience clinical 'transformation' to a more aggressive and rapidly progressive disease termed transformed follicular lymphoma, which is histologically akin to diffuse large B-cell lymphoma.

Transformed follicular lymphoma has a very poor prognosis and is commonly a terminal event. Data collected prospectively over 25 years in the authors' centre, relating to 325 new diagnoses of follicular lymphoma, give a median overall survival of 9.5 years. There was a 28% risk of transformation to histologically proven transformed follicular lymphoma or diffuse large B-cell lymphoma over 10 years, and these individuals had only a 1.2-year median survival from transformation. An advanced stage and high FLIPI score at initial diagnosis were predictive of transformation (Montoto et al, 2007b). Those individuals surviving more than 15 years from diagnosis had a significantly reduced risk of subsequent transformation to diffuse large B-cell lymphoma, further highlighting the heterogeneity of this malignancy.

In symptomatic patients with widespread follicular lymphoma, the aims of therapy at this point are to first eradicate symptoms and improve quality of life. Even a partial response to therapy may alleviate symptoms and herald a period of quiescence with improved quality of life and no treatment. Evidence is accumulating that modern combination therapies may offer a modest survival benefit.

A Cochrane review addressed the question of whether a maintenance schedule of rituximab infusions following a course of chemo-immunotherapy for follicular lymphoma was beneficial (Vidal et al, 2009). Data relating to 895 patients from four clinical trials indicated that overall survival was improved by intermittent maintenance doses of single-agent rituximab. The optimal schedule and duration of rituximab maintenance is yet to be established.

Case study

The patient developed a large abdominal mass 3 years later. Computed tomography-guided biopsy provided histological confirmation of relapsed follicular lymphoma. She received six cycles of R-CVP (rituximab, cyclophosphamide, vincristine, prednisolone) combination chemoimmunotherapy producing a clinical and radiological remission. Her own haemopoietic stem cells were mobilized from the bone marrow with subcutaneous injections of granulocyte colony-stimulating factor, then harvested from the peripheral blood. She was admitted to receive high-dose therapy with autologous haemopoietic stem cell rescue.

High-dose therapy

Current management of recurrent or refractory disease consists of combination chemotherapy, which often contains anthracyclines. Fludarabine has been used to treat patients with relapsed or refractory disease.

Historically, poor impact on overall survival in follicular lymphoma, despite achievement of remissions using conventional doses of chemotherapy, led to exploration of intensifying treatment beyond the doses which would produce myeloablation. Reconstituting normal haemopoiesis with stored progenitors harvested during a period of remission provides 'rescue' from prolonged marrow failure following myeloablative doses of cytotoxic chemotherapy and/or radiotherapy. There is evidence that prolonged freedom from disease recurrence occurs in some patients following this schedule, with survival curves suggesting a plateau after 12 years (Rohatiner et al, 2007). In this retrospective analysis, 121 patients underwent high-dose therapy with autologous stem cell rescue in their second remission, and were followed for a median of 13.5 years; 48% remained in a remission at 12 years. There were 15 deaths attributed to treatment-related myelodysplasia or acute myeloid leukaemia, all in patients who received both cyclophosphamide and total body irradiation, raising concerns about the toxicity of such regimens.

In a European Blood and Marrow Transplantation registry study, retrospective analysis was conducted on 693 patients who received high-dose therapy between 1979 and 1995. Progression-free survival at 10 years was 31%, with younger age and high-dose therapy in first complete remission correlated with improved progression-free survival. Patients receiving total body irradiation had a shorter overall survival and higher non-relapse mortality. Of the 39 who subsequently developed secondary myelodysplasia or acute myeloid leukaemia, 34 had received total body irradiation-containing high-dose therapy regimens. A plateau was again seen in progression-free survival, suggesting potential cure in some patients (Montoto et al, 2007a). The relative merit of high-dose therapy in light of both modern agents such as rituximab, and modern approaches such as reduced intensity conditioning allogeneic stem cell transplantation, is not yet clear.

Case study

The patient attended a routine follow-up clinic with her sister and was found to be well, in an ongoing clinical complete remission. She enquired about future treat-

ments at relapse, and whether she could receive a 'bone marrow transplant' from her sister. After considering the potential risks and benefits, she elected not to proceed to allogeneic stem cell transplantation.

Allogeneic transplantation

Transplanting haemopoietic precursors from an HLA-matched healthy donor can induce an immune response against host tissues, including against a malignant clone. This is termed the graft *vs* leukaemia effect. These precursors are obtained from the peripheral blood after mobilization from the bone marrow into the circulation using subcutaneous granulocyte colony-stimulating factor injections, rather than by direct aspiration of bone marrow itself. Following a period of immune suppression therapy (conditioning), these allogeneic peripheral blood stem cells are infused to the recipient. In the following weeks and months, immune suppression is modified to prevent donor cell rejection, allow the engrafting cells to thrive, while preventing florid graft *vs* host disease. Graft *vs* host disease is the reaction of donor immune cells against normal host tissues, in particular the skin, liver and gastrointestinal tract. While graft *vs* host disease appears linked to the beneficial graft *vs* leukaemia effect, it is harmful when severe. Increased mortality, particularly attributable to infection, is associated with severe graft *vs* host disease and with attempts to modify its course with immune suppression.

In ablative conditioning schedules, myelosuppressive doses of cytotoxic chemotherapy are delivered before allogeneic stem cell infusion. In reduced intensity conditioning schedules, immune suppression alone is delivered, with all the intended anti-lymphoma effect coming from subsequent graft *vs* lymphoma immunity. This graft *vs* leukaemia effect has been demonstrated in vivo, with remissions occurring in response to donor lymphocyte infusions in patients with relapsed follicular lymphoma following allogeneic stem cell transplantation (Morris et al, 2004). Ablative regimens incur longer inpatient stays, a prolonged neutropenic phase, more severe graft *vs* host disease, and consequently greater treatment-related mortality than reduced intensity conditioning regimens. As such, reduced intensity conditioning regimens have enabled older patients and those with comorbidities to benefit from the graft *vs* leukaemia effect. However, even reduced intensity conditioning regimens incur a significant morbidity and mortality, and appropriate patient selection and timing of transplantation is critical in this indolent malignancy. However, follicular lymphoma does remain incurable by both conventional and novel therapies, and so young patients will die of their disease far short of the population average life expectancy. Young patients, and particularly those with rapidly progressive, relapsed or refractory disease, should be involved in discussions about allogeneic transplantation (Toze et al, 2004).

Case study

Two years later the patient remained well, but biopsy of a 2 cm groin node revealed grade II follicular lymphoma. After a further six asymptomatic years of expectant management, she developed a rapidly enlarging mass in her left groin with associated weight loss, fevers and night sweats. Biopsy revealed transformed follicular lymphoma. Remission induction was attempted with anthracycline-containing combination chemo-immunotherapy. This was poorly tolerated, and no response was observed after two full cycles of therapy. The patient elected to receive no further chemotherapy, and received best supportive care at home where she died.

Future possibilities

A better understanding of the pathophysiology of follicular lymphoma is beginning to reveal new prognostic markers which may point the way towards therapeutic targets. The tumour microenvironment, that is the surrounding non-malignant immune cells, supporting stromal cells and matrix, may have an important role in the progression of follicular lymphoma. There is a need to prospectively validate, in clinical trials, data suggesting that the gene expression signature of the infiltrating non-malignant immune cells at diagnosis is strongly predictive of prognosis in follicular lymphoma (Dave et al, 2004). Critical pathways of immune modulation of malignant cell behaviour in follicular lymphoma may be suitable candidates for targeted therapy, and there is already evidence that response to certain existing regimens correlates with the composition of the tumour microenvironment (de Jong et al, 2009).

Therapies based on specific characteristics of the malignant clone are under investigation, including individualized anti-tumour vaccination targeting the immunoglobulin idiotype, a clonal marker expressed on tumour B cells. Successful host production of an anti-idiotype antibody in response to vaccine has been correlated with improved overall survival at 10 years (Ai et al, 2009), but it remains to be established whether this represents a biomarker of host immune competence or truly reflects efficacy of the vaccine.

For the vast majority of patients follicular lymphoma repeatedly responds to therapy but is ultimately incurable. Predicting the point at which further efforts at remission induction are no longer in the individual patient's best interests is difficult. Anticipating end-of-life care issues and timely involvement of palliative care services are important aspects of good clinical practice in this disease.

Conclusions

There remains no clear consensus regarding the fundamental questions of when and how to treat follicular lymphoma. Treatment approaches will continue to evolve in the light of clinical trial data, and as an improved understanding of the underlying pathophysi-

ology of this disease enables identification of rational therapies. It is vital that newly diagnosed patients are offered entry into clinical trials, and that clinical data and diagnostic material are retained for research purposes, whenever possible. BJHM

Conflict of interest: none.

Ai WZ, Tibshirani R, Taidi B, Czerwinski D, Levy R (2009) Anti-idiotype antibody response after vaccination correlates with better overall survival in follicular lymphoma. *Blood* **113***:* 5743–6

Ardeshna KM, Smith P, Norton A et al (2003) Long-term effect of a watch and wait policy versus immediate systemic treatment for asymptomatic advanced-stage non-Hodgkin lymphoma: a randomised controlled trial. *Lancet* **362:** 516–22

Brice P, Bastion Y, Lepage E et al (1997) Comparison in low-tumor-burden follicular lymphomas between an initial no-treatment policy, prednimustine, or interferon alfa: a randomized study from the Groupe d'Etude des Lymphomes Folliculaires. Groupe d'Etude des Lymphomes de l'Adulte. *J Clin Oncol* **15:** 1110–17

Dave SS, Wright G, Tan B et al (2004) Prediction of survival in follicular lymphoma based on molecular features of tumor-infiltrating immune cells. *N Engl J Med* **351:** 2159–69

de Jong D, Koster A, Hagenbeek A et al (2009) Impact of the tumor microenvironment on prognosis in follicular lymphoma is dependent on specific treatment protocols. *Haematologica* **94:** 70–7

Fisher RI, Leblanc M, Press OW, Maloney DG, Unger JM, Miller TP (2005) New treatment options have changed the survival of patients with follicular lymphoma. *J Clin Oncol* **23:** 8447–52

Gattiker HH, Wiltshaw E, Galton DA (1980) Spontaneous regression in non-Hodgkin's lymphoma. *Cancer* **45:** 2627–32

Gribben JG (2007) How I treat indolent lymphoma. *Blood* **109:** 4617–26

Hoppe RT, Kushlan P, Kaplan HS, Roseberg SA, Brown BW (1981) The treatment of advanced stage favorable histology non-Hodgkin's lymphoma: a preliminary report of a randomized trial comparing single agent chemotherapy, combination chemotherapy, and whole body irradiation. *Blood* **58:** 592–8

Horning SJ, Rosenberg SA (1984) The natural history of initially untreated low-grade non-Hodgkin's lymphomas. *N Engl J Med* **311:** 1471–5

Krikorian JG, Portlock CS, Cooney P, Rosenberg SA (1980) Spontaneous regression of non-Hodgkin's lymphoma: a report of nine cases. *Cancer* **46:** 2093–9

Kumar R, Bhargava P, Zhuang H, Yu JQ, Schuster SJ, Alavi A (2004) Spontaneous regression of follicular, mantle cell, and diffuse large B-cell non-Hodgkin's lymphomas detected by FDG-PET imaging. *Clin Nucl Med* **29:** 685–8

MacManus MP, Hoppe RT (1996) Is radiotherapy curative for stage I and II low-grade follicular lymphoma? Results of a long-term follow-up study of patients treated at Stanford University. *J Clin Oncol* **14:** 1282–90

Montoto S, Canals C, Rohatiner AZ et al (2007a) Long-term follow-up of high-dose treatment with autologous haematopoietic progenitor cell support in 693 patients with follicular lymphoma: an EBMT registry study. *Leukemia* **21:** 2324–31

Montoto S, Davies AJ, Matthews J et al (2007b) Risk and clinical implications of transformation of follicular lymphoma to diffuse large B-cell lymphoma. *J Clin Oncol* **25:** 2426–33

Morris E, Thomson K, Craddock C et al (2004) Outcomes after alemtuzumab-containing reduced-intensity allogeneic transplantation regimen for relapsed and refractory non-Hodgkin lymphoma. *Blood* **104:** 3865–71

Muller AM, Ihorst G, Mertelsmann R, Engelhardt M (2005) Epidemiology of non-Hodgkin's lymphoma (NHL): trends, geographic distribution, and etiology. *Ann Hematol* **84:** 1–12

Rohatiner AZ, Nadler L, Davies AJ et al (2007) Myeloablative therapy with autologous bone marrow transplantation for follicular lymphoma at the time of second or subsequent remission: long-term follow-up. *J Clin Oncol* **25:** 2554–9

Solal-Celigny P, Roy P, Colombat P et al (2004) Follicular lymphoma international prognostic index. *Blood* **104:** 1258–65

Toze CL, Barnett MJ, Connors JM et al (2004) Long-term disease-free survival of patients with advanced follicular lymphoma after allogeneic bone marrow transplantation. *Br J Haematol* **127:** 311–21

Vaughan Hudson B, Vaughan Hudson G, MacLennan KA, Anderson L, Linch DC (1994) Clinical stage 1 non-Hodgkin's lymphoma: long-term follow-up of patients treated by the British National Lymphoma Investigation with radiotherapy alone as initial therapy. *Br J Cancer* **69:** 1088–93

Vidal L, Gafter-Gvili A, Leibovici L, Shpilberg O (2009) Rituximab as maintenance therapy for patients with follicular lymphoma. *Cochrane Database Syst Rev*: CD006552

Wilder RB, Jones D, Tucker SL et al (2001) Long-term results with radiotherapy for Stage I-II follicular lymphomas. *Int J Radiat Oncol Biol Phys* **51:** 1219–27

Young RC, Longo DL, Glatsein E, Ihde DC, Jaffe ES, Devita VT Jr (1988) The treatment of indolent lymphomas: watchful waiting v aggressive combined modality treatment. *Semin Hematol* **25:** 11–16

KEY POINTS

- Follicular lymphoma is the most common indolent non-Hodgkin lymphoma.
- Follicular lymphoma typically responds to chemotherapy but subsequently relapses, often responding again on several occasions before ultimately becoming chemorefractory.
- Around 2% of patients per year develop transformed follicular lymphoma, a much more aggressive, rapidly fatal disease.
- Traditional chemotherapy can induce remissions but has little impact on survival.
- Rituximab monotherapy, or its addition to traditional cytotoxic agents, has improved survival.
- High-dose therapy with autologous stem cell rescue in remission can induce long-term survival, at the cost of both short- and long-term toxicity.
- A graft *vs* lymphoma immune effect can be harnessed to induce long-term remissions using allogeneic haemopoietic stem cell transplantation. Reduced intensity conditioning regimens reduce the toxicity of this approach.
- All patients with follicular lymphoma should be considered for clinical trials, as the optimal timing and nature of intervention remains unclear.
- Laboratory investigations into the molecular and genetic abnormalities in follicular lymphoma will hopefully reveal critical therapeutic targets.