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Management of non-aggressive NHL

10. Follicular lymphoma

11. Small lymphocytic lymphoma/chronic lymphocytic leukaemia

12. Marginal zone/gastric MALT lymphoma

10. Follicular lymphoma
Follicular lymphoma is the second most common lymphoma after DLBCL, with an incidence of 4 per 100,000. The median age of patients is around 60 years and approximately 50% of all patients will present with BM involvement (stage IV disease). It is readily treatable but is characterised by a recurring and remitting course over several years with each successive response becoming more difficult to achieve and of shorter duration. Resistant disease or transformation into DLBCL is the usual cause of death. Despite the responsiveness of the disease to chemotherapy, radiotherapy or biological therapy, relapse is usually inevitable even if a CR is obtained, is so the goal of treatment keep the patients symptom free. It is desirable for eligible patients to be recruited to clinical trials.

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Table 10.1 Correspondence between International Working Formulary (IWF) and WHO classification systems of NHL

IWF subtype IWF classification
A Sll
-consistent with Cll
- plasmacytoid

WHO classification
B cell Cll*/Sll

B
C
D

Follicular small cleaved lymphoma
Follicular mixed lymphoma
Follicular large cell lymphoma

Follicular lymphoma
Grade 1: 0-5 centroblasts/high power field (HPF)
Grade 2: 6-15 centroblasts/HPF
Grade 3a, 3b: > 15 centroblasts/HPF
Variants

The Ann Arbor staging classification is not used but advanced stage (Ill or IV) and symptomatic disease are adverse prognostic factors.

10.1 Investigation
Patientswith follicularlymphomausuallypresentwith enlargementof lymphglands.'B' symptomsare rare.Whensymptomsare usuallypresent,theyare one or moreof the B symptoms:fever,nightsweats,or weightloss.

Diagnoses based upon histological and clinical criteria are highly accurate for SLL (84%) and follicular lymphoma (93%). Immunophenotyping improves diagnostic accuracy only slightly, to 87% and 94%, respectively. Most patients (> 80%) with SLL or follicular lymphoma present with advanced stage disease (Ill or IV).

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It is now recognised that follicular large cell NHL (grade 3) should not be regarded as a non-aggressive NHL, given its aggressive clinical course and documented response to anthracycline-based chemotherapy, and should be included in the category of aggressive NHL (see section 5).

10.2 Treatment
The clinical course of Follicular Lymphoma differs considerably between individual patients, and several adverse prognostic factors have been identified. The IPI provides an especially comprehensive model. The IPI was originally devised to classify patients with aggressive lymphomas, but has been shown to apply as well to patients with SLL, follicular lymphoma, and low-grade NHL.

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Figure 10.1 Survival of FC according to IPI

The IPI prognostic model was based upon data from newly diagnosed patients. However, a high IPI score is also a useful indicator of poor prognosis in relapsed patients. Additional negative prognostic factors associated with marked reduction in survival for relapsed patients are a poor objective response to initial therapy, or relapse within 12 months after initial response.

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10.3 Observation

Sinceno survivaladvantagehasbeenshownfor immediatetreatmentcomparedwith expectantmanagementin asymptomatic patientstreatmentcan be delayeduntilsymptomsdevelopor histologicaltransformationoccurs.

10.4 Stage I and 11disease
10.4. 1 Radiotherapy
For 30% of patients who present with stage I and 11disease, involved field irradiation can be curative if the disease is of small volume. At a total dose of 30-40 Gy, 'in-field' relapse is uncommon, and 1O-year DFS of70% can be expected (see section 14). Total nodal irradiation has also been successfully used as initial therapy for patients with stage III disease and as treatment capable of inducing CRs in patients with recurrent or poorly responsive stage III disease. There is no evidence that chemotherapy is better or that its addition to radiotherapy improves survival.

Conclusions and recommendations 10a

. Local radiotherapy remains standard therapy for localis.~d(stage I)follicular lymphoma of small volaj!J1e

. The toxicity of such treatment should be taken into accq!.lntwhen treating completely excised stag~qNHL
Level of evidence IV -grade C.

10.5 Standard therapy for stage Ill/IVdisease
Treatment of advanced (stage III or IV) small lymphocytic lymphoma (SLL), follicular lymphoma is palliative, and therapies are usually administered intermittently over a period of several years. This is conventionally managed with the expectation that the illness will pursue a remitting recurring course, death being due to resistant disease (with or without transformation to DLBCL) or the

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complications of therapy. Hence it is customary to manage the asymptomatic patient expectantly, until an indication for therapy presents itself. The widely accepted 'indication' for disease is overt progression 'bulk' or compromise of a vital organ, especially the BM. The interpretation of the indications for therapy are influenced by the philosophy of the physician and the preference of the patient. There is little evidence to show whether the choice of initial therapy influences the natural history of indolent NHL, and only limited data showing that patients with a poor prognosis benefit from an aggressive initial treatment. Therefore, except in clinical studies, patients with advanced SLL, follicular lymphoma, or low-grade NHL usually receive a conservative initial therapy such as chlorambucil (e.g. 10 mg/day for 6 weeks followed by 3 two-week cycles separated by 2-week intervals). Steroids and vinca alkaloids are also active with response rates of 60% when used alone. Although widely used, there is no evidence that the addition of steroids and vinca alkaloids to alkylating agents improve response or survival. The addition of an anthracycline (e.g. CHOP) will be more toxic and will improve response though not OS in chemosensitive patients. Including anthracycline in first-line treatment combinations is recommended for histological grade 3 follicular lymphoma, since it achieves a higher response rate, but does not improve survival.

The conventional strategy overall is to treat to 'remission' (variously defined), and then manage by regular surveillance until progression, upon which re-staging and repeat biopsy should be performed and the appropriate intervention undertaken. Such an approach leads to a median survival of about 10 years with the majority of patients receiving 3 therapies at about 3-year intervals. Histological grade 3 disease should be managed as an aggressive lymphoma.

Recommendations 10b
Alkylator-based therapies remain standard treatment in follicularlymphomas grades 1 and 2
Anthracyclines increase CR rates but have no impact on DFS or OS
Level of (negative) evidence lIa, lib: strength B

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10.5.1 Alpha interferon
Randomised trials comparing chemotherapy plus interferon (IFN) to chemotherapy alone suggest that outcome depends upon multiple factors, including patient prognosis, the inclusion of anthracycline as a component of chemotherapy, and the IFN treatment regimen. In some trials carried out in patients with poor prognosis or bulky disease, initial treatment with CHVP plus IFN or COPA
plus IFN increased relapse-free and overall survival relative to chemotherapy alone. By comparison, adding IFN to less aggressive chemotherapy such as CVP does not increase OS but may increase relapse-free survival.The recently published SWaG trial showed
no benefit from the addition of low-dose IFN at to intensive induction therapy in terms of either DFS or OS. A meta-analysis of all
previous studies but excluding this last study suggested both an OS and DFS benefit in patients who received both intensive
induction therapy and high alFN (> 36 mU per month).

Initial therapy

Observe

Stage I . Local radiotherapy . CR/
~ Relapse. Treatmentfor stageIII
and IV(see below)

Stage II-IV Initial therapy

Either: Either:
CVP/chlorambucil

(UK standard) 1--+ PR/CR --. Observe
. watch and wait until BNCI criteria
fulfilled (see text)

or

(European standard)
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Follicular Lymphoma

Relapse
Localised disease . Local radiotherapy Stage Ill-IV
Early relapse « 2 years)
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Eligible for PBSC transplant ~ Re-induction
FMD
CHOP

{ Mabthera} Noteligiblefor PBSC transplant

Late relapse (> 2 years) Re-biopsy . Re-treat as for initial therapy

Figure 10.2 Therapy for follicular lymphoma

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10.5.2 Stem cell transplantation (SCT) in first CR
A number of phase 11studies have reported the use of SCT in patients with responsive follicular lymphoma in first CR. In the largest of these trials, patients entering CR or good PR were treated with a regimen based on total body irradiation (TBI) after CHOP induction therapy. A 3-year DFS of> 60% was observed but longer follow-up suggests continuing recurrence and a significant and as yet unexplained incidence of myelodysplasia.

Recently the German low-grade lymphoma study reported the preliminary results of a prospective randomised trial comparing conventional chemotherapy with myeloablative chemotherapy as first-line therapy in patients with follicular NHL. The 2-year DFS of 70% obtained with this approach compares favourably with the 40% DFS obtained with conventional therapy but longer follow-up will be required to confirm this result.

Conclusion and recommendation 10c

There is insufficient evidence to recommend SGT infirst(GR

10.6 Treatment of Relapsed Patients
Response to prior therapy is the most important factor determining subsequent treatment strategy. In general, a short-lived response to treatment requires an increasingly aggressive therapeutic approach although this does not guarantee success. Toxicity, efficacy, and duration of treatment must all be considered as factors in disease palliation.

Prognostic factors are useful as predictors of treatment outcome and the likely evolution of treatment requirements. Many patients with advanced SLL, follicular lymphoma, or low-grade NHL and good IPI scores will respond to repeated courses of GP or GVP therapy with prolonged remission, while patients with poor IPI scores are more likely to have a rapid relapse, and are candidates for early aggressive intervention.

Generally, patients who relapse 2 years or more after treatment with alkylating agents (GP or GVP) will respond to further treatment with the same agents, and there is no

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proven need to escalate therapy. Patients whose disease is not well controlled by alkylating agents may respond to single-agent or combination chemotherapies, biological agents, or radiotherapy.

10.6. 1Anthracycline-based chemotherapy
CHOP, or CHOP-like regimens will induce responses in patients with relapsed indolent NHL. Remissions of approximately 12 months duration have been reported. Administration of multiple courses of anthracycline-based chemotherapy is limited by the cumulative cardiotoxicity.

10.6.2 Purine analogues
Fludarabine phosphate as a single agent, or in combinations such as tludarabine, mitoxantrone, dexamethasone (FMD) may yield beneficial responses in relapsed disease. In several studies, response rates with tludarabine range from 32%-62%. FMD has been reported to induce> 90% response rates, and 47% CRs, in patients with recurrent lymphoma and a good prognosis. Purine analogues are also associated with significant immunosuppression.

10.6.3 Immunotherapy
Rituximab (BCSH Position Paper), a chimeric human/murine IgG1monoclonal antibody, is increasingly used in the treatment of patients with relapsed or chemoresistant follicular NHL.

Rituximab has cytolytic activity directed at B cells, in contrast to the more systemic cytotoxicity of chemotherapy. Rituximab effects cell lysis by way of mechanisms that are distinct from those of chemotherapy, a feature that leads to significant activity in chemoresistant patients. The treatment duration of rituximab monotherapy (4 weeks) is considerably shorter than required for most chemotherapy regimens. Rituximab induces remissions in approximately 50% of patients with relapsed or refractory advanced low-grade or follicular NHL, with median PFS of 9 months. Efficacy is highest in patients without bulky tumours.It is recommended for use in patients who are resistant to or intolerant of chemotherapy.

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10.6.4 Radiotherapy
Although not widely used in the treatment of disseminated NHL, extended field radiotherapy can induce high response rates in patients with relapsed follicular lymphoma, with DFS rates of 65% at 5 years and 37% at 10 years. Limited field radiation is often used palliatively to relieve local symptoms or mechanical problems, or to treat bulky or persistent lesions (iceberg radiation) as a supplement to chemotherapy.

10.6.5/britumomab tiuxetan
Ibritumomab tiuxetan (Zevalin), a murine monoclonal antibody directed against CD20 and bound to 9Oyttrium,a beta emitter, has been utilised as a single agent in refractory and relapsed low-grade NHL. Recently, results of a randomised prospective clinical trial have been reported where ibritumomab tiuxetan has shown improved response rates when compared to rituximab in patients with relapsed low-grade NHL (78% vs 46%). There is as yet no evidence of any impact on PFS.

10.6.6 Other therapies
Ongoing trials in early stages investigating innovative therapies include studies of anti-idiotypic monoclonal antibodies, vaccines and non-myeloablative allogeneic stem-cell transplantation.

Conclusions and recommendations 10d

. There are no definitive therapies for relapsed Follicular NHL

. Re-biopsy to confirm low-grade histology is recommended
Entry into clinical trials should be encouraged to define the role of antibody therapy,, and newer combination chemotherapies inthi~,context

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and aaents used Dreviouslv

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