Guidelines for the Management of Follicular Lymphoma

Scope

The following guidance for first- and second-line therapy applies to follicular lymphoma histological grades 1, 2 and 3a according to the World Health Organisation Classification. Follicular lymphoma grade 3b should be treated according to the guidelines for diffuse large B cell lymphoma.

Background issues

- FL has a very variable clinical course and there is still no reliable way of identifying which patients have aggressive versus indolent disease.
- Except in very elderly or frail patients, the aim of treatment should be to achieve the longest possible progression-free survival with acceptable toxicity.
- All studies conducted so far have shown that adding rituximab (R) to chemotherapy improves the efficacy of different types of first and second-line chemotherapy in terms of response, progression-free survival (PFS) and possibly overall survival (OS).
- The role of R maintenance is still controversial. It seems to prolong PFS after first-line chemo without R and second-line chemo with R but there is no data about its effect following first-line R-chemo (hence the PRIMA trial). Long-term toxicity may also be an issue.
- R-chemo regimens with stronger chemo are more effective but also more toxic.
- Fludarabine regimens are effective but can be very myelosuppressive and may compromise stem-cell harvesting.
- Autografting in first or second response prolongs PFS and OS following chemo without R but it is unclear whether or not it adds anything to R-chemo.
- Allografting is potentially curative in the long term but risky in the short term. The TRM of RIC allografting is about 10-20%, and a quarter to a third of survivors relapse, mostly within the first year.
- Zevalin seems to be highly effective in a proportion of patients but cannot be given in patients with significant BM involvement or post autograft. It has also been associated with profound cytopenias in patients who have received previous fludarabine regimens.
- The toxicity or more aggressive regimens may outweigh any benefit in elderly/frail patients.
- Local radiotherapy (RT) may cure up 50% of patients with stage I/II disease

General comments on management

There is no ‘right’ or ‘wrong’ way to treat follicular lymphoma, and patients and their families should be made aware of this. The pros and cons of each treatment option (including no treatment) should be discussed in full in order to arrive at a sensible way forward that takes into account the clinical behaviour of the lymphoma, age/frailty/co-morbidity, and patient preference.
Localised disease (stage IA and stage IIA involving contiguous sites)

Patients with lymph node masses <5cm should be offered RT irrespective of symptoms, although it is reasonable not to treat asymptomatic elderly/frail patients based on the observation that untreated patients with localised disease seem to do very well. Patients with larger masses should be offered chemotherapy as for more advanced disease.

Advanced-stage disease, no symptoms or complications

Watch and wait, or entry into the NCRI ‘watch and wait’ trial of nothing versus rituximab.

Advanced stage disease, symptoms or complications (actual or imminent)

- Patients can be divided into 3 groups according to youth and fitness. Figures 1, 2 and 3 show specific algorithms outlining recommendations for first- and second-line treatment for each patient group.
- Except for very elderly/frail patients, first-line therapy should be with immunochemotherapy (R-CHOP in young patients, R-CVP in older patients), or entry into the PRIMA study.
- Radiotherapy should be considered for residual masses following chemotherapy. Applicability will depend on (a) size of the residual mass (b) likely toxicity and (c) positivity on PET scanning.
- The choice of second-line therapy should be tailored to the nature of the disease, e.g., for clinically aggressive disease with grade 3a histology, approaches used for aggressive lymphoma are appropriate, whereas fludarabine-based regimens or Zevalin are more appropriate for clinically indolent disease with grade 1 or 2 histology.

References

1. North West Haematology Association Guidelines for follicular lymphoma (available via website)
4. Forstpointner R, Dreyling M, Repp R, et al. The addition of rituximab to a combination of fludarabine, cyclophosphamide, mitoxantrone (FCM) significantly increases the response rate and prolongs survival as compared with FCM alone in patients with relapsed and refractory follicular and mantle cell lymphomas: results

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Fig 1. Young fit patients (i.e. transplantable)

R-CHOP x 6

PR with localised residual mass

CR or PR with multiple residual masses

NR/PD (= aggressive disease)

?Local RT

PBSC harvest if BM clear

Watch & wait

Late relapse
Clinically indolent
Grade 1 or 2 histology

BM clear

Zevalin

BM involved

R-FCM

Early relapse
Clinically aggressive
Grade 3a histology

Salvage chemotherapy
R-DHAP or similar

Response

No response

Transplant

Palliation

BEAM auto

RIC allo
Fig 2. Patients too old/frail to transplant but otherwise well

R-CVP

- PR with localised residual mass
  - ?Local RT
    - Late relapse Clinically indolent Grade 1 or 2
      - BM clear
        - Zevalin
      - BM involved
        - FR
  - Early relapse Clinically aggressive Grade 3a histology

- CR or PR with multiple residual masses

- NR/PD

  - Clinically aggressive Grade 3a histology
    - Watch & wait
      - BM clear
        - Zevalin
      - BM involved
        - FR
  - Clinically indolent Grade 1 or 2
    - BM clear
      - Zevalin
    - BM involved
      - FR
Fig 3. Elderly frail patients