Scottish Follicular non - Hodgkin lymphoma consensus guidelines.

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Consensus group.

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Diagnosis

Diagnosis and subsequent investigation of newly presenting and relapsed patients should follow BCSH Guidelines. It is recommended that both FLIPI (age, stage, haemoglobin, LDH and number of nodal areas) and FLIPI 2 (age, haemoglobin, bone marrow involvement, nodal size and beta-2 microglobulin) be recorded at diagnosis.

First-line treatment

Early stage disease

Defined as stage I and stage II where the nodes are contiguous.

Staging should be confirmed by standard CT scan followed by PET scan where radiotherapy is to be given with curative intent.

There is good evidence to support the use of involved field radiation, which has the potential for cure in a proportion of patients. The evidence to support involved field radiation was published prior to the widespread use of PET to confirm the stage, therefore it is reasonable to expect that cure rates will be at least as high as those stated in the literature.

Stage II- IV asymptomatic disease

Current practice is to “watch and wait”.

The 'Watch and Wait trial' reported in abstract in late 2010 and revealed a benefit in terms of time

to next treatment with rituximab versus “watch and wait”. The median time to initiation of new therapy (chemotherapy or radiotherapy) for patients managed by “watch and wait” was 34 months. However, in patients given rituximab (4 doses of 375 mg/m^2, followed by maintenance every 2 months for 2 years), the median time to initiation of new therapy was significantly longer ($p<0.0001$) and was not been reached after 4 years. However, long-term outcomes are unclear and the quality of life data has not yet reported. There are also concerns around the impact of early rituximab exposure on response to subsequent rituximab containing therapy. Therefore, although the use of rituximab in asymptomatic patients appears promising, rituximab is not licensed or SMC approved for this indication and is not currently recommended.

Stage II - IV symptomatic disease.

Definition of symptomatic disease

The GELF criteria should be used to define symptomatic disease.

GELF criteria

One or more of the following:

- Involvement of 3 nodal sites, each with a diameter of 3 cm.
- Any nodal or extranodal tumor mass with a diameter of 7 cm.
- B symptoms.
- Splenomegaly.
- Pleural effusions or peritoneal ascites.
- Cytopenias (leukocytes < 1.0 x 10 /L and/or platelets < 100 x 10 /L)
- Leukaemia (> 5.0 x 10 /L malignant cells)

First-line treatment.

Initial treatment should be rituximab plus chemotherapy (R-chemo). The use of rituximab in this way is SMC approved [ref: 493/08] [link to SMC approval]. The choice of chemotherapy should be guided by disease characteristics.

The majority of patients will receive R-CVP. Trial data supports the use of 8 cycles in responding patients. It is recognised that this may be replaced in routine practice by chemotherapy to maximal response plus 2 cycles with a likely minimum of 6 and a maximum of 8 cycles.

Evidence directly comparing R-CHOP and R-CVP is not available. It appears that treatment with R-CHOP results in a more rapid reduction in tumour burden and an improved response rate compared

with R-CVP. However, this does not appear to result in an improvement in OS and is associated with greater short-term and potential long-term toxicity. It may also limit treatment choice in patients who subsequently develop transformed disease. The risks and benefits of treatment with R-CHOP should be discussed at the appropriate MDM prior to initiation of treatment.
Recommendations for the use of R-CHOP as first-line are summarised below.

R-CHOP is recommended for patients in whom a rapid response to reduce the tumour burden is clinically important. for example those with significant end-organ compromise. Such patients include those with:

- Hydronephrosis.
- Biliary obstruction.
- Substantial effusions e.g. symptomatic pleural effusion particularly those requiring drainage.
- Gross lymphoedema, particularly in patients with established venous obstruction.
- Symptomatic spinal cord depression causing neurological compromise.

R-CHOP may additionally be considered in patients with a high FLIPI score (3-5) and/or clinically debilitating B-symptoms.

To be eligible for R-CHOP patients need to be formally assessed as to their suitability for anthracycline based treatment. Two cycles of R-CHOP to rapidly reduce tumour burden and alleviate symptoms, followed by R-CVP for the remainder of induction treatment may potentially be an option to reduce toxicity.
It is proposed to carry out a Scotland-wide audit to determine actual first-line treatment in FL and the rationale behind treatment decisions.

Consideration should be given to entry into available first line clinical trials.
Currently available studies.

- PACIFICO for elderly patients [link to protocol].
- GA101/bendamustine study in younger patients [link to protocol].

Patients who are too frail for R-chemo or those in whom an intravenous regimen is impractical should receive oral chemotherapy with chlorambucil and dexamethasone. (SNLG protocol. chlorambucil 20mgs/ M^2 (max 30 mgs) days 1-3 plus dexamethasone 4mgs bd. days 1-5).

Maintenance.

All patients who respond to R-chemo induction should receive R-maintenance.

The PRIMA study [Salles, 2011] supports the use of first-line R-maintenance at a dose of 375 mg/m^2 every 2 months for 2 years or until disease progression. The PRIMA study demonstrated a significant benefit in PFS with first-line R-maintenance over observation alone: 74.9% versus 57.6%, p<0.0001 after a median follow-up of 36 months.

R-maintenance is SMC-approved in this setting [ref: 675/11] [link to SMC approval].

Response assessment.

A CT scan should be carried out half-way through treatment with R-chemo, at the end of induction treatment and at the end of maintenance treatment.

Follow-up.

Follow-up should be carried out according to BCSH Guidelines. Cross sectional imaging is only recommended if there is clinical suspicion of relapse and routine interval scanning is not supported.

Disease progression or relapse.

Progression is defined as :

1. A ≥50% increase from nadir in the sum of the products of the greatest diameters (SPD) of any previously identified abnormal node for partial responders or non-responders.
2. The appearance of any new lesion during or at the end of therapy.

Relapse is defined as :

1. The appearance of any new lesion or increase by ≥50% in the size of previously involved sites.
2. A ≥50% increase in greatest diameter of any previously identified node greater than 1 cm in its short axis or in the SPD of more than one node.

Second-line treatment

- Prior to a treatment decision patients should be re-staged. Re-biopsy should be undertaken where possible, primarily to exclude disease transformation. There should be re-evaluation of the initial biopsy.
- Patients who progress following radiotherapy alone should be evaluated and managed as for newly presenting patients.

Progressive disease following first-line systemic treatment

At present, best available evidence supports the use of appropriate re-induction chemotherapy followed by second-line maintenance treatment of patients who are rituximab naïve or have

received R-chemo alone first-line. There is no evidence to support routine second-line maintenance with rituximab in patients who have already received first-line maintenance.

Progressive disease in rituximab naïve patients.

This is a diminishing group but such patients should enter the treatment algorithm as for newly diagnosed patients.

Progressive disease following R-chemo alone.

- If patients are asymptomatic, "watch and wait" remains appropriate.
- Patients with localised symptomatic relapse may be treated with IF radiotherapy. (Consider FORT study)
- For patients with extensive, symptomatic, CD20+ve, disease treatment should be guided by the length of first response.

Patients previously treated with R-chemo alone with progression on treatment or a response duration of <6 months since last rituximab.

- The choice of R-chemo re-induction should be guided by prior R-chemo treatment.
- For those patients who relapse or progress during or following R-CVP, treatment options include a trial of anthracycline based treatment: R-CHOP given for 3 cycles followed by re-evaluation of response with treatment to 6 cycles in responders.
- An alternative R-chemo based regimen for those unsuitable for anthracycline based treatment. Suitable regimens may include R-FC, R-F or R- CEPP.
- For those patients who relapse or progress during or following R-CHOP, consider transplantation in transplant-eligible patients: typically R-DHAP x 3 followed by LEAM or BEAM autograft or R-chemo in transplant-ineligible patients: R-FC, R-F or R-CEPP.
- Consider entry into a clinical trial if available.

Patients previously treated with R-chemo alone with an off treatment response of >6 months since last rituximab.

- The choice of R-chemo re-induction should be guided by prior R-chemo treatment.
- Patients who received R-CVP first-line may be considered for R-CHOP or R-CVP. Patients who received R-CHOP first-line may be considered for alternative R-chemo combinations.
- For those patients previously treated with R-CVP, treatment options include a trial of R-CHOP given for 3 cycles followed by re-evaluation with treatment to 6 cycles in responders. Alternatively repeat R-CVP 6-8 cycles, depending on response, for those unsuitable for anthracycline based treatment or those patients with a long (> 2 yrs) response off therapy.
- For those patients who previously received R-CHOP consider transplantation in transplant-

eligible patients, typically R-DHAP x3 followed by LEAM or BEAM peripheral stem cell transplant or in transplant-ineligible patients consider R-FC as first-choice or modified as R-F. Stem cell collection should be carried out prior to initiation of R-FC in otherwise transplant eligible patients who are not planned to move immediately to transplant.

- R plus other chemotherapy including bendamustine may become an alternative future option.

Patients with extensive, symptomatic, CD20-ve disease, should receive appropriate chemotherapy regimes including high dose therapy with transplantation but without rituximab, as above.

Maintenance.

R-maintenance should be initiated as part of second line therapy in CD 20 +ve patients previously treated with R-chemo alone and who respond to R-chemo re-induction. R-maintenance is SMC-approved in this setting [ref: 330/06] [link to SMC approval].

Progressive disease during or following first line R-maintenance.

There is a lack of evidence to support treatment decisions in this patient group and the recommendations below are accordingly based on consensus.

- R-maintenance should be discontinued where there is progressive disease and all patients should undergo a further biopsy.
- If patients are asymptomatic, "watch and wait" remains appropriate.
- Patients with localised symptomatic relapse may be treated with IF radiotherapy. (Consider FORT study)
- If patients are symptomatic and CD20+ve, treatment should be guided by time since last exposure to rituximab and choice of first line induction therapy.
- If patients are symptomatic and CD20-ve, chemotherapy without rituximab should be considered.
- There is insufficient data to support a second course of R-maintenance in this patient group.

Patients with progression on maintenance or a response duration of <6 months since last rituximab.

- The choice of R-chemo re-induction should be guided by prior R-chemo treatment.
- For those patients who relapse or progress whose initial treatment was with R-CVP, treatment options include: a trial of anthracycline based treatment. R-CHOP given for 3 cycles followed by re-evaluation of response with treatment to 6 cycles in responders.
- An alternative R-chemo based regimen for those unsuitable for anthracycline based treatment. Suitable regimens may include R-FC, R-F or R- CEPP.

- For those patients who relapse or progress whose initial treatment was with R-CHOP, consider transplantation in transplant-eligible patients: typically R-DHAP x 3 followed by LEAM or BEAM autograft or R-chemo in transplant-ineligible patients: R-FC, R-F or R-CEPP.

- Consider entry into a clinical trial if available.
- Experimental therapy and best supportive care should be provided for those patients with short first response who do not respond to second-line re-induction treatment.

Patients with an off treatment response of >6 months since last rituximab.

- The choice of R-chemo re-induction should be guided by prior R-chemo treatment.
- Patients who received R-CVP first-line may be considered for R-CHOP or R-CVP. Patients who received R-CHOP first-line may be considered for alternative R-chemo combinations.
- For those patients previously treated with R-CVP, treatment options include a trial of R-CHOP given for 3 cycles followed by re-evaluation and treatment to 6 cycles in responders. Alternatively R-CVP 6-8 cycles may be repeated for those unsuitable for anthracycline based treatment or those patients with a long (> 2 yrs) response off therapy.
- For those patients previously treated with R-CHOP consider transplantation in transplant-eligible patients, typically R-DHAP x3 followed by LEAM or BEAM peripheral stem cell transplant or in transplant-ineligible patients consider R-FC as first-choice or modified as R-F. Stem cell collection should be carried out prior to initiation of R-FC in otherwise transplant eligible patients who are not planned to move immediately to transplant.
- R plus other chemotherapy including bendamustine may become an alternative future option although not currently SMC approved.
- Consider trial entry.

Third-line treatment

Patient factors and prior treatment should guide management decisions. The following should be taken into consideration:

- Duration of disease and duration of response.
- Prior treatment.
- Current performance status.
- Histology.

There is no evidence to support repeated administration of R-maintenance.

Transformed disease.

- All patients should be formally restaged and discussed at the MDM.

- In patients who are eligible for transplant, induction with R-DHAP and autologous transplantation should be considered.
- Allogeneic transplantation may have a role.
- Rituximab maintenance should not be used routinely post transplant for transformed disease but may be considered as secondary treatment of the underlying low grade disease component in otherwise eligible patients.
- In patients who are ineligible for transplant, R-CHOP 6-8 cycles is recommended in patients fit enough to tolerate treatment.
- Non-anthracycline based R-chemo is recommended for patients deemed ineligible for R-CHOP.
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Allogeneic transplantation.

Sibling or unrelated donor allogeneic transplantation should be considered in the following scenarios.

- Failure of mobilisation in patients eligible for autologous transplantation.
- Relapse post autograft.
- In patients with a < 6 months duration of response to R-CHOP induction or re-induction as an alternative to autologous transplantation in highly selected individuals.

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