Peer Review Report #1

FOLLICULAR LYMPHOMA

Overall evaluation

Very good and complete review in a field where there are still many controversies. I also agree with the recommendation of adding to the EML Rituximab and Bendamustine for which there are strong data supporting this recommendation.

Proposed additions to the text

1) Transformation: it is stated approximately 45%. This is the upper limit in one study. I would propose, which is more realistic, 30-45 % (the percentage depends on the aggressivity in rebiopsing and in selection biases).

2) Evaluation of tumor burden. It is proposed to use GELF criteria. It should however be noted, that in the vast majority of the centers worldwide hemato-oncologists use rather the FLIPI (Federico M, Bellei M, Marcheselli L et al. JCO 2009; 27:4555-4562)

3) Limited stage FL. Somewhat is the recommendation for giving radiotherapy a bit too strong (also thinking of low income countries). Besides the Stanford data, it should also be added that also in many other databases there is no difference in OS between radiotherapy or observation. So observation should be added under the advised treatment for local disease.

4) Maintenance with Rituximab. The outcome of the RESORT trial recently published should be added. In this trial, patients with low-burden FL were randomized, either to maintenance Rituximab or to Rituximab only at relapse. With a median follow-up of 4-5 years, there is no difference in median time to treatment failure between the two strategies so that the accompanying editorial has as a title “End of Rituximab maintenance for low-tumor burden follicular lymphoma” (Kahl BS, Hong F, Williams et al. Rituximab extended schedule or retreatment trial for low-burden follicular lymphoma: ECOG protocol E4402. J Clin Oncol 2014; 32:3096-3102).

5) Dosage of Bendamustine: the only one indicated is 90 mg/m². There should be however the indication that in elderly, frail or pre-treated patients the dosage should be reduced to 70-80 mg/m² in order to avoid very important haemotoxicity.

6) Discussing the main reasons to commence treatment it is stated “to improve symptoms and/or improve survival”. This is wrong, since no treatment has shown improving survival in patients who have no symptoms or do not have a rapidly progressive disease. So the indication for starting treatment is always to improve symptoms or to avoid complications, in case of rapidly progressive disease. In the discussion of the trials it could also be remembered that there is no trial comparing R-chemotherapy versus R alone followed by chemo in case of relapse. Personally I believe that this trial also would show no difference in the OS.

7) As an overall background, I can add that in Switzerland patients with FL with advanced stage are treated at diagnosis as follows: 30% watch and wait, 40% Rituximab alone, 30% R-chemotherapy.

8) It is correctly stated that outcome in FL has greatly improved in the last 20 years. It might perhaps be added that nowadays in developed countries the median survival, putting all patients with FL together, kjkis in the order of 18 years.