NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Single Technology Appraisal

Rituximab for recurrent or refractory stage III or IV follicular non-Hodgkin's lymphoma (review of TA No. 37)

Expert statement declaration form

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Personal Statement on Technology

I have interpreted the scope of the STA as examining the evidence for the use of rituximab in relapse or refractory follicular lymphoma of stage III and IV.

Increasingly, first line treatment for this condition is the combination CVP-R (cyclophosphamide, vincristine [sometimes vinblastine], prednisolone and rituximab), which produces a high response rate and long remissions in most responders. However, relapse is virtually inevitable.

Second line treatment has varied. Most investigators have been prepared to re-use first-line treatment if the remission has been very long, but otherwise most have used CHOP (CVP plus adriamycin). In more elderly patients and those with any cardiac impairment physicians have tried to avoid the anthracycline and have sometimes opted for a fludarabine-based regimen such as FCM (fludarabine, cyclophosphamide and mitoxantrone). Relapse after this leaves the option of either an anthracycline- or fludarabine-based regimen.

TA37 gave authorization for the use of rituximab for re-induction of remission in patients for whom chemotherapy was unacceptable.

As I see it there are three circumstances where rituximab might be used in relapsed or refractory follicular lymphoma: a] in the circumstances envisioned by TA37; b] in combination with chemotherapy for re-induction of remission; c] as a single agent for the maintenance of remission. I shall briefly review the evidence for each of the three.

a] Revisitation of TA37. As far as I can ascertain there are no new data since TA37. As time has passed and rituximab has been used more an more with chemotherapy, the use of rituximab in this way has diminished, but there are still some patients in whom this is the only option for therapy.

b] Use of rituximab in combination with chemotherapy for re-induction of remission. There have been two trials addressing this problem. EORTC 20981 compared 6 courses of CHOP with 6 courses of CHOP-R as second-line induction therapy (Van Oers et al. Blood. 2006; 108: 3295-3301) and GLSG-FCM which compared 4 courses of FCM with 4 courses of R-FCM as second-line induction therapy (Forstpointner et al. Blood. 2004; 104: 3064-3071).

In the EORTC trial, there was a significantly greater response rate, complete response rate and progression-free survival for patients who received rituximab with their induction chemotherapy. There was also a trend for a greater overall survival at three years in those receiving rituximab (82.5% v 71.9%; p=0.096). Similarly, with the GLSG study there was a significantly better response rate and progression-free survival as well as a trend to wards a longer overall survival in those who received rituximab in their induction regime.

c] Use of single agent rituximab as maintenance therapy. The same trials (Van Oers et al. Blood. 2006; 108: 3295-3301 and Forstpointner R et al. Blood. 2006; 108: 4003-4008) also examined the value of rituximab as maintenance therapy. In the EORTC trial median PFS from second randomization was startlingly better at 51.5 months in the R maintenance arm versus 14.9 months in the observation arm (p<0.001) with the 3-year overall survival also significantly better p=0.011). The GLSG trial shows similar results with an significant progression-free survival for those treated with maintenance rituximab.

Conclusion

As a clinician I am convinced that the use of rituximab as part of the second-line induction therapy and its subsequent us as single agent maintenance therapy produces a significant and worthwhile benefit for patients suffering form follicular lymphoma stage III and IV. Whether that benefit is something that the NHS can afford is for health economists to decide, but the benefit is real.

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Signed:

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