The Royal College of Pathologists
Pathology: the science behind the cure

BSH

Comments on NICE - Appraisal consultation document
Rituximab for the treatment of relapsed or refractory chronic lymphocytic leukaemia

The Appraisal Committee is interested in receiving comments on the following:

• **Has all of the relevant evidence been taken into account?**
YES!

• **Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?**
YES

• **Are the provisional recommendations sound and a suitable basis for guidance to the NHS?**
Yes except for patients who have had rituximab before I believe should be able to have it again.

• **Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of gender, race, disability, age, sexual orientation, religion or belief?**
No

Comments:

Page 3, Section 1.1

Patients who have received rituximab previously should be allowed to be retreated at relapse because:

- evidence in CLL suggests that patients will respond when retreated. Wierda *et al.,* (J Clin Oncol. 2005 Jun 20;23(18):4070-8.) : The overall response rate for all people in the study was 73% and the complete response rate was 25%. For the group who had previously received rituximab monotherapy or combination therapy, the overall response rate was 64% and the complete response rate was 18%.
- rituximab in other lymphoproliferative disorders indicates that re-treatment is effective. There is no reason to suspect that CLL should be different.

- our current NIHR-adopted study (the ARCTIC study) tests the theory that small doses of rituximab (100mg rather than 500mg/m^2) are equally effective. Patients who have received the 100mg dose should be able to receive the full licensed dose of rituximab when they relapse otherwise they could possibly be disadvantaged by entry into the trial
- if durable remission (i.e. 2+ years) occur after FCR then convention would be to use the same therapy again – to go back to FC would be illogical
- patients may have received rituximab monotherapy for other indications (i.e. ITP assoc with CLL or rheumatoid arthritis) and this should not exclude therapy
- Given the relatively similar response rates in patients having been treated previously with rituximab then by extrapolation the cost per QALY for these patients will still be less than £30,000

Page 14, Section 4.4

"It also heard that the publication of guidance 'Rituximab for the first-line treatment of chronic lymphocytic leukaemia' (NICE technology appraisal guidance 174) recommending rituximab plus fludarabine and cyclophosphamide meant that in the future an increasing number of people with relapsed or refractory disease will have had rituximab and fludarabine combination therapy as a first-line treatment. The Committee considered the exclusion of these groups from the clinical trial was a limitation because it meant that the trial population did not reflect all the people with relapsed or refractory disease who would be eligible for rituximab plus fludarabine and cyclophosphamide." Whilst this is true it is unreasonable to expect that many patients in REACH could have had prior rituximab but it seems very likely that such patients will benefit from the addition of rituximab to FC in subsequent treatment episodes and denying them access seems inappropriate. In addition patients are very unlikely to have FCR more than twice so with the current criteria only a minority will be retreated. Expansion of the criteria to rituximab combined with other chemotherapy combinations (i.e. not FC) would require this data to be accepted.

The reported improvement in overall survival for FCR in frontline CLL is encouraging. The improvement in complete remission rate and progression-free survival was similar for the German CLL8 trial as for the REACH study suggesting that with further follow-up REACH may also show a survival advantage.

[redacted]