Professional organisation statement template

Thank you for agreeing to give us a statement on your organisation's view of the technology and the way it should be used in the NHS.

Healthcare professionals can provide a unique perspective on the technology within the context of current clinical practice which is not typically available from the published literature.

To help you in making your statement, we have provided a template. The questions are there as prompts to guide you. It is not essential that you answer all of them.

Please do not exceed the 8-page limit.

About you

Your name: [redacted]

Name of your organisation UK CLL Forum

Are you (tick all that apply):

- a specialist in the treatment of people with the condition for which NICE is considering this technology?
- a specialist in the clinical evidence base that is to support the technology (e.g. involved in clinical trials for the technology)? Yes – I am a member of the Clinical Guidelines Committee of the UK CLL Forum and have been asked to offer an opinion on their behalf.
- an employee of a healthcare professional organisation that represents clinicians treating the condition for which NICE is considering the technology? If so, what is your position in the organisation where appropriate (e.g. policy officer, trustee, member etc.)?
- other? (please specify)

What is the expected place of the technology in current practice?

The standard treatment for patients whose performance status allows is fludarabine/cyclophosphamide combination therapy (UK CLL 4 Trial). There have been many studies adding rituximab to fudarabine based regimens for newly diagnosed patients as outlined below.

Rituximab

Single agent rituximab therapy induces short-term PRs in previously untreated patients with CLL. The use of subsequent maintenance treatment with rituximab in patients responding to initial treatment with the same agent is being evaluated (Hainsworth *et al*, 2003). A randomized phase 2 study in 104 patients (CALGB 9712), comparing fludarabine given with either concurrent or sequential rituximab, showed a higher overall and CR rate for the concurrent regimen but the median response duration and survival have not been reached for either arm after a median follow-up of 23 months (Byrd *et al*, 2003b). In a retrospective comparative study of patients who received fludarabine only (CALGB 9011 study – 178 patients) and fludarabine plus rituximab (both concurrent and sequential – CALGB 9712 – 104 patients) the combination therapy had a significantly better complete response rate (p=0.002), overall response rate (p=0.0003), progression free survival (2 yr probability of survival 67% versus 45% - p<0.0001) and overall survival (2 yr probability of survival 93% versus 81% -p=0.0006) (Byrd 2005).

In a smaller phase II study of 60 untreated CLL patients fludarabine (6 courses – 25mg/m^2 IV for 5 days) was administered and followed a median of 40 days later by rituximab (375mg/m^2 weekly for 4 weeks) (Del Poeta 2005). After fludarabine therapy there was an overall response rate of 92% with 70% CR's. This rose to 78% CR and 93% OR following rituximab therapy – although only 1 patient with stable disease after fludarabine therapy achieved a CR following rituximab therapy. After a median of 27 months of follow-up 16% of patients had relapsed giving an estimated the PFS rate of 68% at 3 years. All thirty-two ZAP 70 negative patients achieved a CR or PR (p=0.001). Similarly there was a significantly higher overall response rate amongst CD38 negative patients (98% versus 84%; p=0.027). There was also a significantly shorter PFS in ZAP 70 positive patients (25% versus 100% at 3 years; p=0.00005) and CD38 positive patients (18% versus 91% at 3 years; p=0.0002). Also somewhat unsurprisingly, patients with less minimal residual disease following both therapies had a longer PFS at 2.5 years (77% versus 36%; p=0.001).

In an update of earlier data 224 previously untreated patients received combination therapy consisting of fluadarabine, cyclophosphamide and rituximab (FCR) (Keating 2005). The overall response rate was 95% (70% complete, 10% nodular partial and 15% partial remission). Two thirds of patients had <1% CD5/CD19 co-expressing bone marrow cells after therapy. Grade3/4/ neutropenia occurred in 52% of course of therapy with about one third of patients suffered at least one infection and 10% neutropenic fever. The probability of treatment failure at 4 years was only 31%. This cohort has recently been further updated (Tam 2008) and showed six year overall and failure free survival to be 77% and 51% respectively. Median time to progression is 80 months (this compares to 42 months for fludarabine/cyclophosphamide – FC therapy as found in the UK CLL 4 trial). The risk of late infection was 10% and 4% for the first and second year of remission and <1.5% per year for the third year onwards.

The German CLL trails group have prematurely stopped their randomised study (CLL 8) of FC combination therapy plus or minus rituximab due to a significantly improved "outcome" in the FCR group. This has not been formally published or peer reviewed but we are expecting to see the data at the American Society of Haematology meeting this December 2008.

The exact role of rituximab in the poorest risk group of CLL patients – notably those with p53 deletions is not fully characterised and better alternatives may be available.

Thus in conclusion rituximab appears to improve the outcome when used in combination with any fludarabine based regimen in newly diagnosed patients. FCR combination therapy has shown to result in more responses – especially complete responses compared to any previously reported regimens used and indeed we expect this to be confirmed when the German CLL 8 study is formally reported. There appears to be no long term sequelae of the FCR combination particularly with regard to infection risk.

The UK CLL Forum treatment guidelines are at this very time being re-written and it is the recommendation of the Guidelines Committee to advocate FCR as upfront therapy for patients whose performance status is adequate. As rituximab has been with us in clinical practice for almost 10 years we would expect this treatment to become available in any centre treating patients with CLL within the UK.

The advantages and disadvantages of the technology

CLL is presently incurable but it has a very variable clinical course. Many studies over the last 20 years or so have addressed increasing therapy. Typically this meant additional chemotherapy which has led to the present UK CLL Forum recommendation of FC combination therapy to newly diagnosed patients (UK CLL 4 Trial). Rituximab has been Licensed for use in low and high grade non Hodgkin lymphoma for many years. Given the relatively poor results in CLL with rituximab monotherapy it has not been widely used in CLL to date. However there has been a growing awareness of the response rates reported from various centres when combining rituximab with other fludarabine based regimen. The present recommended combination therapy of fludarabine/cyclophosphamide was shown to give an overall response rate of 94% but with only a complete response rate of 39% (CLL 4 Trial). This contrasts with 95% overall response and 72% complete response in the study by Tam. In previous studies – Bosch 2005, Moreton 2005) the achievement of a complete response or minimal residual disease status - has been associated with prolonged survival. Hence we would expect the much improved complete remission rate achievable with FCR to translate into improved survival compared to our present standard first line therapy of FC – the German CLL 8 study should ultimately give us the answer but virtually all experts including myself are expecting improved survival to become apparent with time. Hence we would accept previously demonstrated surrogate markers of prolonged survival such as complete remission status as valid.

Any additional sources of evidence

As stated above we all expect to be enlightened when the German CLL 8 study is presented early in December at the American Society of Haematology meeting.

Implementation issues

The fact that we have been able to use rituximab for a number of years for lymphoma has allowed the necessary expertise in its use to become widely disseminated to virtually all hospitals which means if approved it would be readily available to all suitable patients with CLL. Although infusion reactions are not uncommon meaningful clinically relevant side effects are rare. Again we are all now well experienced in the giving, monitoring and dealing with any side effects of rituximab.

Rituximab as a drug is not cheap. To that cost must be added the necessary costs of an additional infusion (nursing time, lines, venous access etc) to what is presently regarded as standard of care FC therapy. Also overheads such as day unit capacity needs to be addressed. However these costs should be well known to NICE through the previous submission to use rituximab for non Hodgkins lymphoma.