Patient/carer organisation statement template

About you

Your name:
Catriona Gilmour Hamilton

Name of your organisation:

LYMPHOMA ASSOCIATION

Are you (tick all that apply):

- ✔ an employee of a patient organisation that represents patients with the condition for which NICE is considering the technology? If so, give your position in the organisation where appropriate (e.g. policy officer, trustee, member, etc)

I have worked for the Lymphoma Association for 10 years, previously in helpline work and for the last 5 years as a writer, largely of information for patients but also for professional journals and other agencies. I have prepared submissions from the Lymphoma Association for 3 previous NICE appraisals. My work keeps me in constant contact with those who have experienced lymphoma, as users play an important role in the development of our publications.

Background

Rituximab has become a cornerstone of therapy for advanced follicular lymphoma. Rituximab is used in a variety of applications, each with differing implications for patients. Because this STA is considering two distinct applications of single agent rituximab, I will discuss the patient perspective on this technology under subheadings pertaining to each application.

Initially, I would like to give some background as to the experience of follicular lymphoma and how individual lives are affected by the illness. I hope this will help the committee to appreciate the significance of the different applications in terms of achieving and maintaining remission.

About follicular lymphoma:

Follicular lymphoma represents 22% of all cases of NHL[1], meaning that around 2100 new diagnoses are made in the UK each year. Most of these people will have advanced disease at the time of diagnosis.

Follicular lymphoma is more likely to occur after the age of 50. Most people are diagnosed between the ages of 60 and 79[2]. The relatively advanced age of people with follicular lymphoma is particularly significant – many people are less able to tolerate toxic therapies, and it is important that the therapeutic options for follicular lymphoma enable clinicians to prescribe according to individual fitness and co-morbidity.

Behaviour

Advanced follicular lymphoma responds to current treatments, but it recurs at increasingly regular intervals, with increasing resistance to available treatment. With current management, intervals between courses of treatment are typically of 18 months – 3 years duration initially, but this interval shortens over time. Most people reach a point, sooner or later, at which they have little or no response to chemotherapy treatment. Remissions between courses of treatment are more likely to be partial than complete, meaning potential persistence of symptoms during these intervals.

Follicular lymphoma is likely to transform into more aggressive illness with continued relapses. Transformed follicular lymphoma is associated with a poor prognosis.

The description of follicular lymphoma as “low grade” or “indolent” belies the fact that it is a debilitating and difficult disease to live with. People with follicular lymphoma live with an incurable disease that is likely, at some uncertain point in the future, to kill them. Although people live with advanced follicular lymphoma for a median period of 7 - 8 years, these years are punctuated by increasingly frequent intervals of toxic and often harrowing treatments. For many, the disease will fail to go into remission at all, or will relapse quickly and progress rapidly.

Symptoms

Follicular lymphoma can cause a range of symptoms in affected individuals. Most people experience fatigue. Fatigue has a significant impact on quality of life – reduced capacity to work and care for others, increased irritability and anxiety, increased risk of depression, reduced libido, reduced capacity for social interaction and reduced enjoyment of life.

Other symptoms are wide ranging, and depend on what parts of the body are affected by the lymphoma. These include, drenching night sweats, fever, anaemia, and shortness of breath.

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[1] Armitage et al, Journal of Clinical Oncology, 1998 16:2780-2795

[2] Office for National Statistics, Welsh Cancer Intelligence and Surveillance Unit, ISD Online and Northern Ireland Cancer Registry quoted by Cancer Research UK www.cancerresearch.org/types/nhl/incidence accessed June 11 2007

Living with Uncertainty

One of the principle psychological burdens of follicular lymphoma is uncertainty. Those with advanced follicular lymphoma live with a life threatening condition that never really goes away. They know that they will need to undergo prolonged and unpleasant courses of chemotherapy at increasingly regular intervals in the future and that the treatment is increasingly unlikely to work. People with follicular lymphoma are pretty certain that their illness will kill them, but uncertain about when this will happen. This uncertainty can be a constant source of anxiety. Depression is a common problem for people with follicular lymphoma. Uncertainty and loss of hope in the future make it difficult for people to enjoy what time they have.

1. What do patients and/or carers consider to be the *advantages* of the technology for the condition?

Rituximab as remission induction in refractory or relapsed advanced follicular lymphoma:

Rituximab has been used as a single agent to treat relapsed or refractory follicular lymphoma for ten years, and still has a role in this context in spite of its now more regular use in combination with chemotherapy. Single agent rituximab can induce remission and improvement in symptoms, even in patients whose disease has had a poor response to chemotherapy.

Single agent rituximab has a particular role to play in the treatment of patients who have other co-morbidities making them unsuitable candidates for chemotherapy. The clinicians we consulted in preparation for this submission made it clear that there is still an important role for single agent rituximab, particularly for those who are frail and too unwell to cope with chemotherapy. Those in second or subsequent relapse are also likely to have disease that will fail to respond to chemotherapy.

Some patients favour single agent rituximab in this setting because it has the potential to induce remission with none of the toxic side effects of chemotherapy. These patients will already have undergone at least one and probably more than one course of chemotherapy, with all the toxicity and disruption to quality of life that chemotherapy entails. The importance of quality of life for people with advanced follicular lymphoma is paramount. For those unable or unwilling to face further chemotherapy, it is of immense comfort to know that there is a treatment option that might induce remission with little impact on quality of life.

It is imperative that patients and clinicians have access to a variety of treatment options for advanced follicular lymphoma so that treatment can be tailored to the individual and his or her choice.

The benefits of inducing remission with single agent rituximab include:

- Few toxic side effects and relatively short duration of treatment
- Improvement in fatigue
- Improvement in debilitating and unpleasant symptoms of disease, including night sweats, pain, diarrhoea, shortness of breath
- Greater capacity to care for oneself – particularly pertinent given that follicular lymphoma is largely a disease of older people
- Greater capacity to return to work – reduced financial worry, reduced financial dependence, reduced reliance on financial assistance
- Greater capacity to fulfil other personal responsibilities such as caring for children and caring for ageing relatives.

Rituximab as maintenance therapy in adults with relapsed/refractory follicular lymphoma responding to induction chemotherapy with or without rituximab.

Clinical trials affirm that single agent rituximab for maintenance has important clinical outcomes in its licensed setting. It results in a marked improvement in progression free survival – a median PFS in excess of 4 years, compared to just over one year in the observation arm[3] - and improved 3 year overall survival[4]. It also results in higher proportions of people attaining complete remission[5].

These results are achieved with relatively little inconvenience to the patient. Treatment is once every three months, meaning a visit to hospital for a treatment lasting 4 hours or less. Toxicity is relatively minimal. Infusion related side effects are the most common and are usually well managed with administration of paracetamol and antihistamine.

The importance of progression free survival cannot be overstated. If a person has a limited life span, it is of enormous value to spend as little of that time as possible undergoing active treatment. Prolonged PFS represents a landmark improvement in the experience of the illness, and the outlook for those living with it. Imagine what it means to someone having treatment to hope that remission might last 4 years or more, compared with the expectation of only 18months before more treatment will be necessary.

Remission in any cancer is associated with psychological difficulty, in particular the fear that once treatment has finished the disease will return. These difficulties are particularly acute for those with follicular lymphoma, because the disease is almost certain to return at some point in the relatively near future. Relapse is frightening and distressing, and patients would argue that it becomes harder to bear with each relapse, because each time the chances of a successful outcome are significantly reduced.

Patients will take immense reassurance from having treatment that has a proven capacity to prolong remission. It will enable them to feel that their disease is being actively controlled rather than passively waiting for it to come back.

Longer progression free survival means:

- longer periods without symptoms of disease, including fatigue
- people are spared the distress of relapse for longer periods
- less time spent attending hospital
- less time spent undergoing treatment
- greater reassurance in the immediate future and improved mental health
- greater capacity to work – reduced financial worry, reduced financial dependence, reduced reliance on financial assistance
- greater capacity to fulfil other personal responsibilities such as caring for children and caring for ageing relatives.
- improved quality of life.

Better rates of complete remission will mean:

- higher proportions of people having complete eradication of symptoms

[3] Van Oers MH, et al, 'Rituximab maintenance improves clinical outcome of relapsed/resistant follicular non-Hodgkin lymphoma in patients both with and without rituximab during induction: results of a prospective randomized phase 3 intergroup trial', *Blood,* 2006 Nov 15;108(10):3295-301.
[4] ibid
[5] Van Oers et al, 2006

- improved quality of life.

The improvement in overall survival is, quite clearly, something that gives great hope to those with advanced follicular lymphoma. Improvements in survival have eluded clinicians and patients for decades. People facing a terminal illness obviously welcome longer life, even if the potential number of years to be added is relatively few.

We have always stressed the importance of quality of life and the significance of time without treatment in assessing the relative worth of a technology. The advantage in this case is that prolonged life is made possible without compromise to - and with enhancement of - quality of life because of improvements in progression free survival.

2. What do patients and/or carers consider to be the *disadvantages* of the technology for the condition?

Rituximab as remission induction in refractory or relapsed advanced follicular lymphoma:
There are no disadvantages to treatment with rituximab for refractory or relapsed follicular lymphoma. Its side effects are easy to tolerate and it is administered with relatively little interference with day to day life.

Rituximab as maintenance therapy in adults with relapsed/refractory follicular lymphoma responding to induction chemotherapy with or without rituximab.

The administration of a maintenance dose of rituximab for the duration of two years leaves the patient depleted of healthy B lymphocytes. This has the potential to place the patient at greater risk of bacterial infection, but to date there is no evidence to suggest that this risk translates into recurrent severe infection[6]. B-lymphocytes return to normal once maintenance therapy ends. Patients would still opt to have maintenance rituximab in the licensed setting. The risk of future infection would seem worth taking if the remission from lymphoma might be significantly prolonged, and overall survival improved.

3. **Are there differences in opinion between patients about the usefulness or otherwise of this technology?**

Rituximab as remission induction in refractory or relapsed advanced follicular lymphoma:
Patients feel that there should be more treatment options available, particularly treatments that are targeted and with manageable toxicity.

Patients would agree that single agent rituximab has a role to play in treating relapsed disease, particularly for those with disease that fails to respond to chemotherapy, or those reluctant or unable to have further chemotherapy because of its toxicities.

Rituximab as maintenance therapy in adults with relapsed/refractory follicular lymphoma responding to induction chemotherapy with or without rituximab.

There is no difference of opinion as to the value of maintenance therapy. People with advanced follicular lymphoma live with a chronic condition and become well informed about advances in treatment. People are aware of the encouraging results achieved with maintenance therapy, and they know that clinicians worldwide are enthusiastic about its potential.

[6] Solal-Celigny, P., 'Safety of rituximab maintenance therapy in follicular lymphoma', *Leukaemia Research,* 2006 Mar;30 Suppl 1:S16-21

At the Lymphoma Association's recent annual conference, there was recurring discussion of this issue, and many patients were anxious to learn about the use of maintenance rituximab and why it was not yet available in NHS hospitals. There is, to my knowledge, no difference of opinion among patients as to the value of rituximab maintenance in the licensed setting, and I can't imagine that any patient would decline the treatment if it offered the prospect of prolonged progression free and overall survival.

4. Are there any groups of patients who might benefit more from the technology than others? Are there any groups of patients who might benefit less from the technology than others?

Anyone with CD20+ve follicular lymphoma stands a chance of responding to treatment with single agent rituximab. Some people will experience responses of better quality and longer duration than others, but to my knowledge it is difficult to identify these people at the outset.

5. Comparing the technology with alternative available treatments or technologies

(i) Please list any current standard practice (alternatives if any) used in the UK.
For remission induction in second or subsequent relapse:

Standard practice for people in this situation would be limited to further courses of chemotherapy, which will be chosen according to what the person had had before, their response to prior treatment, and other co-morbidities. Chemotherapy options include Chlorambucil, CVP, CHOP, Fludarabine and fludarabine-based combinations, and more toxic 'salvage' regimens such as ESHAP.

For people who have disease that is refractory to chemotherapy, there will be few treatment options other than single agent rituximab or best supportive care. Radioimmunotherapy has a demonstrated capacity to induce remission in such patients[7] but is available to very few NHS patients at present.

For maintenance of remission after chemotherapy induction:

The only other therapy aimed at consolidation of remission is high dose chemotherapy and autologous stem cell transplant.

In other parts of Europe, the use of interferon is more common in this context. However, UK clinicians are less enthusiastic about interferon as maintenance therapy, and patients find it difficult to tolerate. For these reasons it is not standard UK practice.

(ii) If you think that the technology has any **advantages** for patients over other current standard practice, please describe them.

For remission induction in second or subsequent relapse:

[7] Witzig, et al, 'Long-term responses in patients with recurring or refractory B-cell non-Hodgkin lymphoma treated with yttrium 90 ibritumomab tiuxetan', *Cancer,* 2007 Mar 22;109(9):1804-1810 [Epub ahead of print]

Single agent rituximab is associated with far fewer side effects than the chemotherapy regimes listed. It is therefore more suitable for those who are frail, or have co-morbidities that exclude further treatment with chemotherapy.
Combination chemotherapy is associated with many unpleasant side effects including neutropaenia, hair loss, nausea, vomiting, oral mucositis, diarrhoea and peripheral neuropathy. Rituximab is associated with infusion-related side effects, typically fevers, back pain, and flu-like symptoms, particularly with the first dose. Patients feel that these ill effects are far easier to tolerate than the side effects of intravenous chemotherapy, and are usually well managed with antihistamine and paracetamol.

A course of single agent rituximab is also far more convenient for the patient, and less disruptive to day to day life. It requires only four visits to hospital over a 4 week period, compared with many months of treatment with chemotherapy.

The difficulty of constant trips to hospital should not be understated. People often need to travel a considerable distance. Journeys by public transport can be tiresome, circuitous and prolonged. Journeys, whether by car or public transport, cannot usually be managed alone. Older people, who may live alone or in comparative isolation, can find it difficult to access assistance with transport for months at a time. Travel to hospital costs money in fares, petrol, and particularly parking.

Hospital admission is frequent with repeated doses of chemotherapy. Hospital admission has a massive impact on a person's quality of life. It means that people are removed from home and loved ones. For older people, hospital can be a disorienting and potentially dangerous experience, associated with the risk of infection, injury, and reduced independence after discharge.

For maintenance of remission after chemotherapy induction:

Maintenance rituximab has many quality of life advantages compared with high dose therapy and stem cell transplant. It is far less toxic, it is administered with minimal disruption to day to day life, and to date it would appear that it can be safely administered for a two year period[8], although there is more to be learnt about its long term impact.

High dose therapy and autolgous stem cell transplant is, by contrast, highly toxic, prolonged, unpleasant, and very expensive in terms of NHS resources. It is associated with long term physical and mental ill effects, including post traumatic stress disorder, prolonged fatigue, and reduced capacity for full time employment. People often cite a period of 1 – 2 years recovery following high dose therapy.

Of course, high dose therapy and ASCT is suitable for a very small proportion of patients with advanced follicular lymphoma, which is largely a disease of old age. Rituximab therapy is well tolerated by all age groups.

(iii) If you think that the new technology has any **disadvantages** for patients compared with current standard practice, please describe them. Disadvantages might include:

Single agent rituximab has no particular disadvantages over standard therapies in either application.

Research evidence on patient or carer views of the technology

[8] Van Oers MH, 'Rituximab maintenance therapy: a step forward in follicular lymphoma', *Haematologica.* 2007 Jun;92(6):826-33; Solal-Celigny, P., 'Safety of rituximab maintenance therapy in follicular lymphoma', *Leukaemia Research,* 2006 Mar;30 Suppl 1:S16-21

If you are familiar with the evidence base for the technology, please comment on whether patients' experience of using the technology as part of their routine NHS care reflects that observed under clinical trial conditions.

The patient experience of rituximab as remission induction in routine care is consistent with that observed in clinical trials.

Rituximab maintenance therapy is not, to date, part of routine NHS care.

Are you aware of any research carried out on patient or carer views of the condition or existing treatments that is relevant to an appraisal of this technology? If yes, please provide references to the relevant studies.

The Lymphoma Association is currently supporting a study at the CRUK and UCL Cancer Trial Centre in London: 'Watch and Wait and Quality of Life'. An initial description of this study, by June Warden, Lymphoma Association Quality of Life Research Co-ordinator, which includes a discussion of patient's views about living with follicular lymphoma, can be found at:

http://www.lymphoma.org.uk/hottopic/June%20Warden/june%20warden.htm

Availability of this technology to patients in the NHS

What key differences, if any, would it make to patients and/or carers if this technology was made available on the NHS?

I have outlined the advantages to patients of this technology at question 1 above.
The continued availability of single agent rituximab for induction of remission in second or subsequent relapse will enable patients and clinicians to tailor treatment to the individual and to individual choice. This is of particular pertinence in managing a disease that affects people in later life.

The availability of maintenance rituximab in its licensed indication would, in addition to the advantages of prolonged periods without disease, be of immense psychological importance to patients in terms of their capacity to enjoy life and their hope in the future.

What implications would it have for patients and/or carers if the technology was **not** made available to patients on the NHS?

People with follicular lymphoma are regular users of the National Health Service. On the whole they are passionate advocates for it, but they care about its standards. They expect lymphoma treatment in the United Kingdom to equal that of anywhere else in the world, and are aware that maintenance rituximab is more widely available in Europe and the USA. Patients expect that their clinicians should have access to the treatments that they know will give them the best chance of prolonged disease free life.

It is of immeasurable importance to people that they have faith in the quality of the care they get in NHS hospitals. To lose this faith would add intolerable stress and anxiety to people already dealing with a grave and often distressing situation. Failure of the NHS to match international standards would be devastating for patients.

People with follicular lymphoma gain hope from the knowledge that treatment of this condition is improving. They emphasise how important this hope for the future is to them, even if it is a future that they will not participate in themselves.