Patient/carer organisation statement template

MAINTENANCE RITUXIMAB FOLLOWING INITIAL IMMUNOCHEMOTHERAPY FOR PATIENTS WITH ADVANCED FOLLICULAR LYMPHOMA

About you

Your name:

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.

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

Rituximab maintenance therapy following an initial course of immuno-chemotherapy has the potential to improve remission, to prolong remission, and to give people with follicular lymphoma longer periods of life free from disease.

Initially, we would like to give some background information about what it is like to have follicular lymphoma and how individual lives are affected by the illness. We hope this will help the committee to appreciate the value to patients of potentially prolonging first remission.

About follicular lymphoma:

Follicular lymphoma represents 20 – 30% of all cases of NHL, meaning that around 2500 new diagnoses are made in the UK each year. Most of these people will have advanced disease at the time of diagnosis. Current life expectancy for advanced disease is between 8 and 10 years depending on prognostic indicators such as age and burden of disease.

Follicular lymphoma is more likely to occur after the age of 50. Peak incidence occurs between the ages of 60 and 79[1].

The relatively advanced age of people with follicular lymphoma has particular significance. It is important that therapeutic options are tolerable for people who, as a result of co-morbidities, may not be sufficiently fit for more toxic therapies. It is also important to maintain remission for as long as possible to reduce the need for treatment of relapsed disease. Many of the symptoms of follicular lymphoma, particularly fatigue, will exacerbate some of the day to day difficulties of later life.

Behaviour

Many people with advanced follicular lymphoma will not need treatment initially. These are people with no symptoms, and with no indication of compromised organ or bone marrow function. A significant proportion of these people will live without treatment for as many as 10 years.

It is a rare individual who lives without treatment altogether, and the majority will reach a point at which treatment becomes necessary. Standard treatment to induce remission is a combination chemotherapy combined with rituximab. The chemotherapy regimens in use in the UK are typically CHOP, CVP and FCM. All are associated with significant toxicities, in particular myelosuppression and resultant neutropaenia, mucositis, peripheral neuropathy and hair loss.

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 2 – 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, with repeated relapse, into more aggressive illness. 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

[1] Office for National Statistics, Welsh Cancer Intelligence and Surveillance Unit, ISD Online and Northern Ireland Cancer Registry quoted by Cancer Research UK www.info.cancerresearch.org/cancerstats/types/nhl/incidence accessed July 28, 2010

likely, at some uncertain point in the future, to kill them. Although people live with advanced follicular lymphoma for a period of some years, these years are punctuated by increasingly frequent intervals of toxic treatments. For some, the disease will fail to go into remission at all, or will relapse quickly and progress rapidly.

Symptoms

Advanced follicular lymphoma can cause a range of symptoms.

Most people experience **fatigue**, an experience that can be markedly debilitating and can have a significant impact on quality of life.

Fatigue can prevent a person from being able to care for themselves: it can prevent people from climbing the stairs to the bathroom; it can make it difficult to get in and out of a bath; it can make it hard to prepare a meal. Even if these things are accomplished, an individual may be left without the energy for other daily activities.

Fatigue results in reduced capacity to work, reduced ability to care for others, increased irritability and anxiety, increased risk of depression, reduced libido, reduced capacity for social interaction and reduced enjoyment of life.

Given the advanced age of many follicular lymphoma patients, fatigue exacerbates the complications of ageing, frailty and social isolation.

Other symptoms are wide ranging. Follicular lymphoma can involve the bone marrow, resulting in reduced blood cell production. This can cause anaemia – which will worsen symptoms of fatigue – shortage of platelets and shortage of white blood cells. Other symptoms of lymphoma include, drenching night sweats, fever, and weight loss.

Follicular lymphoma can affect many sites around the body and symptoms will depend on what parts of the body are involved. For example, involvement of lungs can result in pleural effusion, causing acute chest pain and difficulty breathing. Involvement of abdominal nodes or gastro-intestinal tract will cause pain, change in bowel habit, indigestion and anorexia.

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 may never really go away.

Those who do not need to be treated immediately have to live with a cancer when nothing is being done about it. Reassurances that initial therapy does not necessarily make a difference to outcome are of scant comfort to people cultured to believe in the importance of treating cancer as early as possible. For many, the knowledge that treatment is inevitable – and the question mark over precisely when it will be needed - pervades everyday life and can get in the way of enjoying their time relatively free of symptoms.

This uncertainty persists after active treatment has begun, following which people with advanced follicular lymphoma will anticipate repeated courses of chemotherapy at increasingly regular intervals in the future, with the knowledge that the treatment is increasingly unlikely to work.

These uncertainties 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. **Advantages**

The key objective in management of advanced follicular lymphoma is to maximise the amount of time that people are in remission, in order to limit the need for treatment with chemotherapy. Maintenance rituximab following initial immune-chemotherapy makes a significant contribution to achieving this objective, and significantly improves the immediate outlook for people with advanced follicular lymphoma.

Maintenance rituximab offers longer remissions. This means longer periods of time without disease and longer periods of time before further treatment is necessary. Longer remissions mean better quality of life:

- longer periods of life without unpleasant treatment
- longer periods without being troubled by fatigue
- longer periods without other unpleasant symptoms of disease
- 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 and potential reduction in financial dependence
- greater capacity to fulfil other personal responsibilities such as caring for children and caring for ageing relatives.

Over the course of two years it offers an improved chance of converting from partial to complete remissions. This means that more people will move from having partially active disease to inactive disease, with subsequent improvement in symptoms and quality of life.[2]

The importance of progression free survival (PFS) 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 18 months before more treatment will be necessary.

One of the principal benefits is the psychological relief of knowing that something is being done to make remission as long as possible. Remission in any cancer is associated with psychological difficulty, and fear of the disease returning at an unnamed point in the future. These difficulties are particularly acute for those with follicular lymphoma, because it is almost certain to come back at some point. Patients will take immense reassurance from having treatment that has a proven capacity to prolong remission. Increased confidence in their immediate future will enable patients to more fully participate in life.

This is achieved with relatively little toxicity or inconvenience to the individual. Treatment is once every eight weeks, meaning a visit to hospital for a treatment lasting 4 hours or less. Toxicity is relatively

[2] Salles, G.A. et.al., 'Rituximab maintenance for 2 years in patients with untreated high tumor burden follicular lymphoma after response to immunochemotherapy', *Journal of Clinical Oncology* 28:15s, 2010 (presented at the American Society of Clinical Oncology annual conference, June 2010, abstract 8004)

minimal. Infusion-related side effects of flu-like symptoms such as shivers, chills and headaches are the most common and are usually well managed with administration of paracetamol and antihistamine.

The PRIMA[3] study demonstrated superior responses to those seen in maintenance therapy for second and subsequent relapse, offering further justification for its use following initial therapy.

This development means that those people newly diagnosed with advanced follicular lymphoma can be offered greater reassurance that those diagnosed up until now. They can be told that they may not need treatment for some time, but that when they do need treatment it will be followed up with therapy to make their remission far longer than would have been expected before. This will make the years ahead less frightening, and less uncertain, and will represent a valuable step forward for people with this illness.

2. **Disadvantages**

Please list any problems with or concerns you have about the technology.

The PRIMA study demonstrated that those having maintenance rituximab experienced more adverse events than those having no maintenance, as would be expected. Adverse events were usually infections. However, the increase in adverse events did not mean significant numbers of people dropping out of the study, and the quality of life data suggest that maintenance therapy did not have a negative effect.

It is known that 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 significant numbers of people troubled by recurrent severe infection.

Patients would still opt to have maintenance rituximab in the licensed setting, in spite of chronic reduction in healthy B lymphocytes. The risk of future infection would seem worth taking if the remission from lymphoma might be significantly prolonged.

3. Are there differences in opinion between patients about the usefulness or otherwise of this technology? If so, please describe them.

People with advanced follicular lymphoma live with a chronic condition and become well informed about advances in treatment. People are now aware of the encouraging results achieved with maintenance therapy. There is, to our knowledge, no difference of opinion among patients as to the value of rituximab maintenance in the licensed setting. It is hard to 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?

There are no subgroups likely to enjoy superior benefit that we are aware of.

In the PRIMA study, the benefit was seen equally across all subgroups.

[3] Salles GA, et al.

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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, and a small proportion will not tolerate rituximab, but it is difficult to identify these people at the outset.

Comparing the technology with alternative available treatments or technologies

NICE is interested in your views on how the technology compares with existing treatments for this condition in the UK.

(i) Please list any current standard practice (alternatives if any) used in the UK.

The only other therapy aimed at consolidation of remission in people with advanced follicular lymphoma is high dose chemotherapy and autologous stem cell transplant. However, this approach could hardly be described as standard practice. Most people with follicular lymphoma are ineligible for high dose therapy as a consequence of age and co-morbidity.

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 new technology has any **advantages** for patients over other current standard practice, please describe them.

Maintenance rituximab has many advantages compared with high dose therapy and stem cell transplant.

Rituximab 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, although there is more to be learnt about its long term impact. It does not cause any of the side effects associated with chemotherapy – hair loss, infection risk, mucositis, anorexia, diarrhoea, nerve damage.

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 the risk of dying during the immediate post transplant phase as a result of infection or other complications of treatment. 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.

No disadvantage compared with alternatives.

Research evidence on patient or carer views of the technology

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.

Patients are currently prescribed maintenance rituximab following second line therapy. The experience of patients concurs with the experience documented in clinical trials. Maintenance therapy is well tolerated and easy to fit in with everyday life.

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?

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. NHS availability would ensure equity of availability of maintenance rituximab regardless of address or individual wealth.

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 the demonstrated benefits of maintenance rituximab mean it is rapidly becoming standard practice.

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.