Patient/carer organisation statement template

Thank you for agreeing to give us your views on the technology and the way it should be used in the NHS.

Patients and patient advocates can provide a unique perspective on the technology, which is not typically available from the published literature.

To help you give your views, we have provided a template. The questions are there as prompts to guide you. You do not have to answer every question. Please do not exceed the 8-page limit.

About you

Your name: Jane Barnard

Name of your organisation:
Chronic Lymphocytic Leukaemia Support Association (CLLSA)

Are you (tick all that apply):

- ✓A patient with the condition for which NICE is considering this technology?
- A carer of a patient with the condition for which NICE is considering this technology?
- 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)
- ✓other? (please specify)

  Chairman, **Chronic Lymphocytic Leukaemia Support Association**
  Presently under treatment with R-FC for first line CLL.

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

1. **Advantages**

(*a) Please list the specific aspect(s) of the condition that you expect the technology to help with. For each aspect you list please describe, if possible, what difference you expect the technology to make.*

Presently, NICE is approving R-FC (Rituximab with Fludarabine and cyclophosphamide) for first line treatment of CLL. CLL is incurable. Patients in whom CLL develops to the point where treatment is needed may leave remission in their lifetime and will require subsequent treatments.

Treatment for relapsed CLL will fall into two broad categories, those patients who did not have R-FC for first treatment, and those (a much smaller group at present) who did.

Rituximab addition to FC and other chemotherapy combinations has been used in other countries for many years. Rituximab is used to treat not only CLL but other haematological conditions, as well as rheumatoid arthritis and lupus. There is both study data and patient anecdotal evidence for R-FC in CLL. What every patient seeks, when they need treatment, is a long lasting remission. To the patient, ideally this means time feeling well, being able to live their lifestyle of choice, making plans and carrying them out. Rituximab combination therapy results in longer, deeper remissions.

This holds true for suitable patients in both the group that has not had R-FC before, and has been reported anecdotally in the group that has had rituximab first line treatment.

Increasing length of survival in CLL is difficult to show since the natural history of the disease gives a long median survival. Hence, evidence from trials would be superseded by that from newer drug combinations before statistical proof was obtained of increased length of patient survival. Increase in progression free survival is used as a predictor for the standard QOL.

By increasing the time between treatments, the number of treatments given to the patient population as a whole will fall. This extrapolates to less expense overall.

Rituximab is excellent for reducing the size of lymph nodes- often within 24 hours of initial treatment. The relief from bulky, possibly uncomfortable or painful nodes is most welcome. Cosmetically, the patient who has been aware of their visible nodes sees an improvement, and self confidence can be restored.

(b) *Please list any short-term and/or long-term benefits that patients expect to gain from using the technology. These might include the effect of the technology on:*

- *the course and/or outcome of the condition*
- *physical symptoms*
- *pain*
- *level of disability*
- *mental health*
- *quality of life (lifestyle, work, social functioning etc.)*
- *other quality of life issues not listed above*
- *other people (for example family, friends, employers)*
- *other issues not listed above.*

Benefits;

- An increase in progression free survival time.
- Physical symptoms connected to bulky glands will be relieved; less pain, discomfort, better ease of movement when lymph glands have impaired joint function. Night sweats will not occur; as the patient recovers from the treatment, fatigue should reduce. Muscle cramps will be less frequent.
- Some immunological problems such as abnormal sensitivity to insect bites will resolve. In time (the immune system has to recover) the patient should be less susceptible to infections.
- Level of disability will reduce as the patient recovers from treatment. Some benefits such as reduction of fatigue and node bulk can be rapid; others such as relative freedom from infection can take longer.
- Mental health is linked to the patient's degree of independence, their expectation of a long remission, and their appearance.

As independence increased, mental health will increase; the patient perceives that they are more able to contribute to the family, socially, and often in a work situation.
Remission time is very precious; a 2 year remission rather than a one year remission means that the time feeling well is greatly increased over the recovery time from treatment.
Patients often feel that their appearance is enhanced. Increased self image leads to more confidence socially.

- Quality of life; anecdotally QOL during a remission is much greater than that of a patient who feels ill and believes that chemotherapy will be necessary in the near future.
- Ability to work; some patients are able to work and long remissions will enhance this. This benefits employers since they are retaining an experienced and well trained employee.
- Social functioning; patients are able to rejoin social groups such as hobby groups, gym, dancing and religious meetings. This is immensely valuable for the patient.
- Any increase in the patient's health and ability to contribute, to work and to follow interests will have a positive benefit for the patient's family. It will also decrease the time which the family has to spend caring for the patient.

- Many patients have functions as carers themselves. Their enhanced ability to care and to cope has repercussions with their family, their dependant, and above all socially.

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

2. Disadvantages

Please list any problems with or concerns you have about the technology. Disadvantages might include:

- aspects of the condition that the technology cannot help with or might make worse.
- difficulties in taking or using the technology
- side effects (please describe which side effects patients might be willing to accept or tolerate and which would be difficult to accept or tolerate)
- impact on others (for example family, friends, employers)
- financial impact on the patient and/or their family (for example cost of travel needed to access the technology, or the cost of paying a carer).

- The overall disadvantage that may arise from R-FC is that some serious side effects occur in a small number of patients. These include delayed onset neutropenia and reactivation of Hep B virus in sufferers. The patient should be well educated by the clinician so that an informed choice can be made. All chemotherapy carries risk, including FC alone, and chlorambucil.
- Most of the conditions (viral, fungal and bacterial infections) that occurred in early recipients of R-FC are well understood and are much less likely to be suffered by patients who have not received multiple types of chemotherapy. Where the clinician perceives a risk, then the appropriate prophylactic drugs can be given. Patients are counselled when to contact the hospital with symptoms of infection. Allopurinol is almost universally given for protection of kidney function, which is checked before treatment.
- Rituximab is given by infusion under controlled conditions, so necessitates a hospital day patient visit.
- As with all treatments, the well informed patient is better able to cope with possible problems, and so are the family.
- The most serious side effect is the combination known to patients as ‘shake and bake’; chills, low blood pressure, rigours, fever; Breathing difficulties can occur which can be life threatening. Prophylactic drugs are given to prevent this, and close monitoring is used. Generally, but not universally, this only occurs on the first infusion.
- The R-FC will make the patient feel unwell. There are recognised peaks and troughs over the 4 week cycle. All chemotherapy, including chlorambucil, the so called ‘gentle’ treatment causes degrees of illness.
- The R-FC can lower the neutrophils to such an extent that a greater interval is necessary between treatments for the patient to recover. This is a consequence of the treatment being effective, and has no overall effect on cost, except for extra blood tests.
- The cost of travel, and the time involved, must be added to patient costs since they will have extra hospital visits for the treatment. Most people find this acceptable, since the UK is relatively small.
- There is always the possibility of travel difficulties affecting people in rural areas, education in the fact that the GP can arrange transport would help.
- In some cases a carer will be needed, particularly when the patient has a young family, or the elderly patient who has outlived friends and has no immediate

family. I would argue that a carer or extra help would be necessary in these cases no matter what chemotherapy was required.

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

In patient meetings in the UK there has been overwhelming support for the concept of R-FC being added to the treatments that the NHS physicians can use. Reading the web anecdotes by patients and carers world wide, there are differences in opinion. Patients have received Rituximab in various combinations and have experienced varying degrees of success. Overall, patient statements are positive. However it is not possible to ascertain whether these patients would receive rituximab under the criteria that have been developed over the last 5-6 years from clinical trials and treatment experience. For example, some non UK treatment centres have a reputation for being less conservative than the EU in their treatment criteria.

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 three areas to consider here.
Firstly, the relative fitness of the patient. Almost regardless of age a fit patient with few or no other conditions would be more able to withstand the rigors of R-FC. Most patients are in fact elderly, and are more likely to suffer from co-morbidities which could make treatment with R-FC inappropriate
Previous treatment with R-FC would also be a factor; if the patient had relapsed after R-FC in less than 2 years then the clinician may consider a different treatment as more appropriate, more likely to succeed
Similarly, if the CLL proves to be resistant to R-FC, or the CLL has been shown to lack the TP53 pathway (an indicator that R-FC may not be the most effective treatment) then other treatments may be selected.
CLL is a disease in which the cancer cells from different individuals, or even clones of cells from one individual, can have different defective or deleted genes and react to drugs in different ways.
It is known that CLL cell lines change as the disease develops. This adds to the difficulties in planning clinical trails particularly in patients who have had previous chemotherapy. Various authors have described the criteria on which treatments can be selected. Because of this, and the monitoring that patients receive during treatment, it is unlikely that R-FC would be prescribed to patients who would not benefit from it.
There are many 'diagnostic markers' described for CLL cell lines some of which have been linked with rapid disease progression (IgVH unmutated, TP53 deletion/mutation)or slower progression, (13q del) but there are studies emerging which seem to be differentiating some gene deletions with sensitivity or resistance to some of the drug combinations. This is a field that is developing rapidly, and will assist the clinician to tailor the treatment to the patient. However, TP53 deleted patients will derive a benefit from R-FC treatment, even if it is not as effective as in some other patient groups

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.

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

Chlorambucil- often used in patients with significant co-morbidities, or kidney problems.
Fludarabine and Cyclophosphamide, (FC) standard first line treatment for fit patients before the introduction of R-FC for first line by NICE (Fludarabine monotherapy is seldom used).
Campath –Alemtuzumab (for TP 53 deleted cases, and when R-FC proves an ineffective treatment.
CHOP, often R-CHOP as CHOP is also used when the CLL does not respond to R-FC or some other combinations.
Transplant- mini-allo, matched unrelated donor (mud) transplants have a good success rate, followed by sibling matched donors. Transplant is preceded by intensive conditioning. Transplant is generally considered a salvage treatment, but some centres consider it appropriate for fit patients at first relapse.
Steroids are often used with any of the above to drop the white cell count or in cases of AIHA.

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

- *improvement in the condition overall*
- *improvement in certain aspects of the condition*
- *ease of use (for example tablets rather than injection)*
- *where the technology has to be used (for example at home rather than in hospital)*
- *side effects (please describe nature and number of problems, frequency, duration, severity etc.)*

As previously stated:

- Patients will remain in remission for longer.
- Patients will be symptom free for a longer time.

The key point here is that clinicians have the experience to use R-FC second line when it is appropriate and will have an advantage for the patient, choosing among the available options

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

- *worsening of the condition overall*
- *worsening of specific aspects of the condition*
- *difficulty in use (for example injection rather than tablets)*
- *where the technology has to be used (for example in hospital rather than at home)*
- *side effects (for example nature or number of problems, how often, for how long, how severe).*

The regime is more difficult that the usual alternative, FC in that drug infusion in a day hospital must be used for the rituximab.
Side effects are similar to FC; in addition, a small number of patients develop delayed onset neutropenia, and a small number develop mucosal problems.

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.

With only a small number of UK patient examples where the patient has obtained the drug through private medicine, the R-FC combination seems to have been very successful and in some cases long remissions have resulted

Are there any adverse effects that were not apparent in the clinical trials but have come to light since, during routine NHS care?

No; rituximab has been used for some time for many conditions and the adverse effects are well recognised. I would emphasise that nursing staff should be made especially aware of potential problems for CLL patients, since they are not as common when rituximab is used to treat other conditions.

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.

There are three studies that have an indirect bearing.

1. Comprehensive Management of the CLL Patient: A Holistic Approach Tait D. Shanafelt and Neil E. Kay *Hematology 2007 (ASH)*

2. Quality of life in chronic lymphocytic leukaemia: an international survey of 1482 patients.Br J Haematol. 2007 Oct;139(2):255-64 Shanafelt TD, Bowen D, Venkat C, Slager SL, Zent CS, Kay NE, Reinalda M, Sloan JA, Call TG.

Both of these studies show a surprisingly low QOL for CLL patients, given the fact that the survival times are so long, and that the disease is treatable. Shanafelt and Kay suggest longitudinal studies, and the original Shanafelt et al study suggests that patients in treatment have lower QOL; intuitively, patients post treatment has a higher QOL.

3. Patients' experience of chronic lymphocytic leukaemia: baseline health-related quality of life results from the LRF CLL4 trial. Else M, Smith AG, Cocks K, Richards SM, Crofts S, Wade R, Catovsky D. (Pub med abstracts) -shows findings to 'support the recommendation to begin treatment when patients experience symptomatic disease, to improve HRQoL'. None of the studies differentiate on type of treatment

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?

To the patients, their carers and families this treatment would make a huge difference. Although conventional wisdom says that the first remission is the best, the indications from the REACH trial and anecdotal evidence suggests that R-FC for relapsed patients increases progression free survival. Not only the fact but the knowledge of the fact would improve the QOL for patients, carers and their families.

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

I am still getting mails and phone calls from members who feel very badly let down that the NHS is not providing the level of care that they feel is reasonable in an advanced country. In the main, these are educated people; I do not disagree with an elderly person who has had a 30+ year career with the NHS when she states that she feels it is unreasonable to refuse her R-FC for second line treatment, when getting private treatment will take most of her savings. If R-FC second line is not granted, then it reinforces the perception of ageism in treatment options

Are there groups of patients that have difficulties using the technology?

Of those suitable for R-FC, there will be people who have travel difficulties. This can be overcome with local support.

Other Issues

Please include here any other issues you would like the Appraisal Committee to consider when appraising this technology.