Clinical Commissioning Policy Proposition:

Addition of Rituximab to first-line standard chemotherapy for CD20 positive B-cell precursor Acute Lymphoblastic Leukaemia (adults)

Reference: NHS England 1748

Prepared by NHS England Specialised Services Clinical Reference Group for Chemotherapy

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Contents

1 Executive Summary

Equality Statement

Promoting equality and addressing health inequalities are at the heart of NHS England's values. Throughout the development of the policies and processes cited in this document, we have:

- Given due regard to the need to eliminate discrimination, harassment and victimisation, to advance equality of opportunity, and to foster good relations between people who share a relevant protected characteristic (as cited under the Equality Act 2010) and those who do not share it; and
- Given regard to the need to reduce inequalities between patients in access to, and outcomes from healthcare services and to ensure services are provided in an integrated way where this might reduce health inequalities

Plain Language Summary

About CD20 positive B-cell precursor acute lymphoblastic leukaemia

CD20 positive B-cell precursor acute lymphoblastic leukaemia is type of acute lymphoblastic leukaemia (ALL), which is a very rare and aggressive cancer of the blood and bone marrow. Although the condition is most common in children, teenagers and young adult, it can affect people of any age (Cancer Research UK, 2018). It is estimated that approximately 300 adults are diagnosed with ALL per year.

The condition is caused by a genetic change in the stem cells which in turn causes immature white blood cells, called lymphoblasts or blast cells, to be released into the bloodstream. The presence of blast cells in the bloodstream leads to a wide variety of symptoms, including tiredness, breathlessness and excessive bleeding and an increased risk of developing infection. People with this condition require immediate treatment.

About current treatments

Chemotherapy is the main treatment option, however, some people may also need treatment with a targeted cancer medicine and/or a stem cell transplant. The duration of treatment for the condition is around two to three years and consists of

several months of intensive multi-drug chemotherapy, followed by low intensity maintenance therapy.

There are a number of different chemotherapy medicines that can be used to treat the condition, each with a unique toxicity and side effect profile. This means that treatment choice can be individualised. There are also marked differences in the treatment protocols for people aged ≤24 years, 25-60 years, and people aged >60 years. These differences are based on the findings of key clinical trials conducted in the United Kingdom.

Stem cell transplantation is an intensive procedure and therefore is only an option for people who are able to tolerate the treatment. Where it is an option, it is often incorporated into first-line treatment in order to consolidate the results of chemotherapy.

About the new treatment

Rituximab is a chimeric monoclonal antibody that targets CD20 protein on the surface of B-cells and destroys them. It is not licensed for the treatment of CD20 positive precursor B-cell acute lymphoblastic leukaemia.

In adults, the presence of CD20 in the cancer cells is associated with disease relapse and poor prognosis. Because of this, the addition of rituximab to first-line standard chemotherapy is considered to offer some distinct benefits, particularly in reducing the rate of disease relapse and the need for further, more costly treatments.

What we have decided

NHS England has carefully reviewed the evidence to treat CD20 positive B-cell precursor acute lymphoblastic leukaemia with rituximab added to standard chemotherapy as first line treatment for adults. We have concluded that there is not enough evidence to make the treatment available at this time.

2 Introduction

This document describes the evidence that has been considered by NHS England in formulating a proposal to not routinely commission the addition of rituximab to standard chemotherapy for the first-line treatment of CD20 precursor B-cell acute lymphoblastic leukaemia (ALL) in adults.

For the purpose of consultation NHS England invites views on the evidence and other information that has been taken into account as described in this policy proposition.

A final decision as to whether the addition of rituximab to standard chemotherapy for the first-line treatment of CD20 positive precursor B-cell ALL will be not routinely commissioned will made by NHS England following a recommendation from the Clinical Priorities Advisory Group.

3 Proposed Intervention and Clinical Indication

Clinical indication

Precursor B-cell ALL, which is a type of ALL, is a very rare heterogeneous haematological disorder that is characterised primarily by an overproduction of immature lymphocytes (called lymphoblasts) in the bone marrow.

The clinical signs and symptoms associated with the condition are either a consequence of bone marrow failure or the consequence of having too many abnormal white blood cells. These include: (i) general weakness; (ii) fatigue or tiredness; (iii) bruising; (iv) weight loss; and (v) swollen lymph nodes (Cancer Research UK, 2018).

Treatment options are individualised and driven by a number of different factors, including age, cell characteristics, protein (CD20) expression and the presence of any genetic mutations, such as the Philadelphia chromosome which normally

means that a targeted cancer drug will need to be given as part of chemotherapy treatment.

First line chemotherapy treatments will normally consists of 9-12 months of intensive multi-drug induction, consolidation and intensification chemotherapy (including steroids, vincristine, asparaginase, daunorubicin or doxorubicin, cytarabine, cyclophosphamide, etoposide, intrathecal methotrexate) to target blasts in the central nervous system. This is followed by low intensity maintenance therapy (with oral 6-Mercaptopurine and Methotrexate) for up to three years (Yorkshire and The Humber Clinical Networks 2016). Allogenic haematopoietic stem cell transplantation is generally offered after completion of induction/intensification therapy, where complete remission has been achieved.

Treatment protocols for all types of ALL in England are based on the results of key clinical trials:

- People aged ≤24 years are treated according to the standard arm of the UKALL 2011 protocol;
- People aged 25-60 with Ph-negative de-novo B-ALL are treated according to the standard arm of the UKALL14 protocol; and
- People aged >60 years are treated according to the UKALL60+ protocol.

The treatment of all types of ALL in adults is challenging because the disease can be resistant to chemotherapy and older people can have a reduced treatment tolerance (Linker et al 2002, Rowe 2005). While the majority of people will have a response to multi-agent induction chemotherapy, with complete remission (CR) rates as high as 93%, most of these people will relapse and ultimately succumb to their disease. The 5-year overall survival (OS) is about 29% to 41% in adults with ALL, with most of the deaths attributed to relapse and significant treatment related complications (Horvat et al 2018). Preventing disease relapse is therefore clinically important.

<u>Proposed intervention</u>

Rituximab is a chimeric monoclonal antibody that targets CD20 on the surface of B-cells. Rituximab is routinely used in the treatment of patients with other B cell malignancies (e.g., lymphomas and chronic leukaemias) and can be safely added to chemotherapy regimens. It is given intravenously as an infusion. It is not licensed for this indication.

Although the majority of B cells express the CD20 antigen, it is only present on 30 to 50% of precursor B-cell ALL blasts. Expression of CD20, a type of protein, has been shown to be an independent predictor of relapse in adult patients (Zhou et al 2012, Maury et al 2016) and is therefore clinically important. The inclusion of rituximab within chemotherapy regimens is designed to improve prognosis and prevent disease relapse, which is the most common cause of death, by targeting CD20 on the surface of B-cells.

It is also considered that by preventing disease relapse, fewer people will need to undergo further and more expensive chemotherapy treatment, which currently includes both Blinatumomab and Ponatinib.

4 Definitions

Cancer – are abnormal cells that divide in an uncontrolled way and can spread elsewhere in the body.

CD20 antigen – is a protein expressed on normal and malignant B cells during nearly all stages of differentiation. It may be found in higher than normal amounts in certain types of B-cell lymphomas and leukaemias.

Chemotherapy – is a cancer treatment where medication is used to kill the cancer cells and is a type of systemic therapy. There are many different types of chemotherapy medication. They all work in a similar way by stopping cancer cells reproducing, which prevents them from growing and spreading in the body. Chemotherapy also affects healthy cells and this can cause side-effects, which will vary depending on the type of cell affected.

Minimal residual disease (MRD) – the name given to small numbers of leukaemic cells (cancer cells from the bone marrow) that remain in the patient during treatment or after treatment when the patient is in remission (no symptoms or signs of disease). It is the major cause of relapse in cancer and leukaemia.

Philadelphia chromosome or Philadelphia translocation (Ph) – a specific genetic abnormality in chromosome 22 of leukaemia cancer cells.

Systemic therapy – are treatments for cancer using substances that travel through the blood stream to reach and affect cells all over the body. Chemotherapy, immunotherapy and targeted agents are types of systemic therapy.

5 Aims and Objectives

This policy proposition considered: the addition of rituximab to first line standard chemotherapy for newly diagnosed CD20 positive precursor B-cell ALL (adults).

The objectives were to: establish, via an evidence review,

- The evidence of clinical and cost effectiveness for the addition of rituximab to first line chemotherapy for Philadelphia negative and positive CD20 positive precursor B-cell ALL;
- The most effective treatment schedule using rituximab, including the total number of doses, in first line treatment of Philadelphia negative and positive CD20 positive precursor B-cell ALL;
- Whether the proportion (%) of antigen expressed in CD20 positive precursor B-cell ALL predicts the response to rituximab immunotherapy; and
- Whether the clinical and cost effectiveness of treatment of CD20 positive precursor B-cell ALL varied by subgroup.

6 Epidemiology and Needs Assessment

ALL is a rare cancer. It can occur at any age, but is more prevalent among children than adults. In the UK, there were 832 reported new cases of ALL in 2015 and 300 of these were in adults (Cancer Research UK 2018).

B-ALL is the most common type of ALL, accounting for 75% of all cases in adults (Pui et al, 2006). Although the majority of B cells express the CD20 antigen, it is only present (defined as ≥20% leukaemic cells expressing CD20 as measured by immunohistochemistry) on 30-50% of B-cell precursor ALL blasts. As a result, it is estimated that between 68 to 113 patients would be eligible for the addition rituximab to standard first line chemotherapy treatment.

7 Evidence Base

NHS England has concluded that there is not sufficient evidence to support a proposal for the routine commissioning of this treatment for the indication.

Four papers were identified fulfilling the criteria for the evidence review: one systematic review, one randomised controlled open-label phase III trial (GRAALL-2005R; n = 209), one non-randomised open-label phase II trial (n = 282) and one economic evaluation study. The systematic review reported data from the phase III trial only; the findings from the systematic review are therefore presented under the data for this study.

What is the evidence of clinical and cost effectiveness for the addition of Rituximab to first line chemotherapy for Philadelphia negative and positive CD20 positive B-cell precursor ALL?

Addition of rituximab to first line chemotherapy for Ph-negative CD20 positive B-cell precursor ALL, after a median follow up of 30 months, resulted in a significant improvement in event free survival (EFS) in the GRAALL-2005R study (hazard ratio (HR) 0.66; 95% confidence interval (CI) 0.45 to 0.98; p = 0.04). At 2 years EFS rates were: rituximab 65% (95% CI, 56 to 74) v control 52% (95% CI, 43 to 63). At 4 years EFS rates were: rituximab 55% (95% CI, 46 to 66) v control 43%

(95% CI, 34 to 55). It also resulted in an increase in 3-year complete remission duration (CRD) in the phase II study (67% v control 40%; p = 0.002). These results were due to a significant reduction in relapse rates (sub distribution HR; this was not defined in the study, 0.52; 95% CI, 0.31 to 0.89; p = 0.02). The cumulative incidence of relapse was estimated to be at 2 years 18% (95% CI, 11 to 27) versus 32% (95% CI, 22 to 42) and at 4 years 25% (95% CI, 16 to 35) in the rituximab group versus 41% (95% CI, 30 to 51) in the control group.

The improvements in EFS, relapse rate and CRD did not result in any significant improvement in overall survival (OS) in either of the studies. Maury et al (2016) reported overall survival: Rituximab 61% vs. control 50%; HR, 0.70; 95% CI, 0.46 to 1.07; p = 0.10). At 2 years OS rates were: rituximab 71% (95% CI, 62 to 80) v control 64% (95% CI, 55 to 74). At 4 years OS rates were: rituximab 61% (95% CI, 52 to 72) v control 50% (95% CI, 41 to 62). However in a post hoc sensitivity analysis by censoring of the data at the time of transplantation for patients who received an allogeneic transplant during first remission, overall survival was longer in the Rituximab group than in the control group (HR 0.55; 95% CI, 0.34 to 0.91; p = 0.02). Thomas et al reported no significant difference in overall survival rates: (Rituximab 61% v control 45%; p = not significant (NS)). However, in a subset analysis in younger patients (age ≤ 60 years) overall survival was significantly improved in the Rituximab group (Rituximab 70% v control 38%; p < 0.001).
It is important to note that the GRAALL-2005A study had a primary endpoint of event free survival and not overall survival and hence was not powered to detect significant OS advantage between both arms. The primary endpoint was met with a significant EFS, which is a highly relevant outcome in this disease and the OS (P=0.1) was trending in favour of the rituximab arm versus control arm.

The overall incidence of severe adverse events did not differ significantly between the groups (rituximab 96% vs. control; 92%; p = 0.72). Although infection was slightly more frequent in the rituximab group, the difference was not significant; rituximab 71% vs. control 55%; p = NS. Allergic reactions to asparaginase were less common in the Rituximab group (2% vs. 11%; p = 0.002). It is not clear why this was the case and hence how it might affect the interpretation of the results.

These results should be treated with caution because of the design and methodological flaws in the studies. The study by Maury et al (2016) was randomised, but the details of randomisation and concealment were not reported. It was an open label study and patients were assessed by the investigators, not by an independent assessor. This could have created some bias in the results. The study by Thomas et al (2010) was prospective, but the patients were not randomised into groups. The control patients were all treated under a different chemotherapy protocol from the Rituximab group and there were a number of protocol changes over the course of the study.

In the paper by Nam et al (2018) the incremental cost-effectiveness ratio of addition of rituximab to standard chemotherapy was calculated at Canadian $21,828 (~£12,308) per quality adjusted life year (QALY) with a 98% probability of being cost effective. The effectiveness was based on GRAALL-2005R, and costs were based on expert opinion and the perspective of a publicly funded Canadian health system. The accuracy of the effectiveness assessment could therefore have been impaired by the limitations in this study. Furthermore, the costs collected from a Canadian health system are unlikely to apply to the UK health service.

Indeed two major differences need to be highlighted between the Canadian health system and the UK system, both of which will reduce the QALY significantly:

1. The paper by Nam was not based on the cost of rituximab biosimilars, which have been used routinely in the UK since 2017; and

2. The paper by Nam assumed that only 25% of all patients with relapsed/refractory ALL would receive blinatumomab during second salvage. In England, every patient with relapsed/refractory Ph-ve ALL is now receiving blinatumomab as first salvage, and most patients with Ph+ve ALL are now receiving ponatinib until progression as first salvage. Both those treatments are increasing the cost of salvage therapy dramatically.

What is the most effective treatment schedule using rituximab, including the total number of doses, in first line treatment of Philadelphia negative and positive CD20 positive B-cell precursor ALL?

No studies were identified comparing different rituximab schedules using rituximab as first line treatment in Ph-negative or positive CD20 positive B-ALL.

Does the proportion (%) of antigen expressed in CD20 positive B-cell precursor ALL predict the response to rituximab immunotherapy?

No studies were identified that evaluated how the proportion of antigen expressed in CD20 positive B-ALL predicts response to rituximab immunotherapy. All the studies included patients based on CD20 expression of 20% or more, but results were not reported by different degrees of CD20 expression.

Does the clinical and cost effectiveness of treatment of CD20 positive B-cell precursor ALL vary by subgroup?

Thomas et al carried out a subset analysis to assess the influence of rituximab in younger CD20 positive patients by excluding the older patients (≥60 years). Significant improvements in 3-year CRD rates (70% v 38%; $p< 0.001$) and OS (75% v 47%; $p = 0.003$) favouring Rituximab were observed.

No studies were identified that evaluated the relative cost-effectiveness in different subgroups.

Conclusion

The addition of rituximab to standard chemotherapy (with or without intensification) significantly increases event-free survival and 3-year complete remission duration in Ph-negative CD20 positive B-ALL. These benefits are mostly due to a significant reduction in relapse rates leading to a trend towards improvement in overall survival. Post hoc subgroup analysis suggests that overall survival might be improved in younger patients. However these results were based on open-label

studies with no proper concealment from investigators; therefore the lower reliability of such analyses makes interpretation uncertain.

The administration of rituximab in this setting is well tolerated with no increase in risk of adverse events seen in the one study that reported this.

Limited economic study data show that the treatment is potentially cost-effective. However, there are uncertainties regarding the applicability of the quality of life data employed in this analysis and the relevance to the UK. Costs were calculated from the perspective of a Canadian publicly funded healthcare payer, which is not necessarily applicable to the UK health service, due to two main differences: (i) the availability of rituximab biosimilars; and (ii) the use of blinatumomab as first salvage therapy in relapsed/refractory ALL in the UK.

8 Documents That Have Informed This Policy Proposition

- NHS England Evidence Review 1748. Addition of Rituximab to standard chemotherapy for newly diagnosed CD20 positive B-cell precursor Acute Lymphoblastic Leukaemia;
- National Institute of Health and Care Excellence (NICE) Technology Appraisal Guidance 450. Blinatumomab for previously treated Philadelphia-chromosome-negative acute lymphoblastic leukaemia; and
- NICE Technology Appraisal Guidance 451. Ponatinib for treating chronic myeloid leukaemia and acute lymphoblastic leukaemia.

9 Date of Review

This document will lapse upon publication by NHS England of a clinical commissioning policy for the proposed intervention that confirms whether it is routinely or non-routinely commissioned.

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