MANAGEMENT IN CONFIDENCE

CLINICAL PRIORITIES ADVISORY GROUP
02 09 2020

Agenda Item No	2.1
National Programme	Cancer
Clinical Reference Group	Chemotherapy
URN	1748

Title
Addition of Rituximab to first-line standard chemotherapy for CD20 positive B-cell precursor acute lymphoblastic leukaemia (ALL) (Adults)

Actions Requested	1. Support the adoption of the policy proposition.
	2. Recommend its approval as an IYSD.

Proposition
The policy proposition recommends that rituximab should be made routinely available for the treatment of CD20 positive B-cell precursor acute lymphoblastic leukaemia (ALL). The policy proposition has been developed in line with the standard Methods for developing clinical commissioning policies. It was initially proposed as not for routine commissioning, however, was unsupported by stakeholders at engagement and public consultation. Following feedback during these stages regarding the efficacy of the treatment, the proposition was reconsidered by the Specialised Services Clinical Panel and revised for routine commissioning. The revised routine commissioning policy proposition was subject to further engagement in July 2020 to 'sense-check' and confirm the new proposed treatment criteria. For this reason, there is an additional engagement report for this.

Clinical Panel recommendation
The Clinical Panel recommended that the policy progress as a routine commissioning policy.

The committee is asked to receive the following assurance:	
1.	The Head of Clinical Effectiveness confirms the proposal has completed the appropriate sequence of governance steps and includes an: Evidence Review; Clinical Panel Report.

2.	The Head of the Cancer Programme confirms the proposition is supported by an: Impact Assessment; Consultation Report; Equality and Health Inequalities Impact Assessment; Clinical Policy Proposition. The relevant National Programme of Care has approved these reports.
3.	The Director of Finance (Specialised Commissioning) confirms that the impact assessment has reasonably estimated a) the incremental cost and b) the budget impact of the proposal.
4.	The Clinical Programmes Director (Specialised Commissioning) confirms that the service and operational impacts have been completed.

The following documents are included (others available on request):	
1.	Clinical Policy Proposition
2.	Consultation Report and Engagement Report
3.	Evidence Summary
4.	Clinical Panel Report
5.	Equality and Health Inequalities Impact Assessment

No	*Metric*	*Summary from evidence review*
1.	Survival	Overall survival is the proportion surviving for the duration that patients were followed up in the study or for a particular time period. Maury et al (2016) is the more reliable study because patients were randomised to the two treatment groups. The study reported no significant difference in overall survival between those patients that had Rituximab and those who had standard chemotherapy alone. 71% of patients in the Rituximab group survived 2 years compared with just 64% of patients in the control group. 61% of Rituximab patients survived 4 years compared with 50% in the control group. The difference was not statistically significant: HR 0.70 (95% CI, 0.46 to 1.07; p = 0.10). This means that the evidence does not show that Rituximab improves overall survival when added to first line therapy for B cell precursor acute lymphoblastic leukaemia (B-ALL). However the results have to be treated with caution because this was an open-label study. In addition, there was not assessment of the statistical power of this study to measure significant differences in overall survival
2.	Progression free survival	Not measured.
3.	Mobility	Not measured.

4.	Self-care	Not measured.
5.	Usual activities	Not measured.
6.	Pain	Not measured.
7.	Anxiety / Depression	Not measured.
8.	Replacement of more toxic treatment	Not measured.
9.	Dependency on care giver / supporting independence	Not measured.
10.	Safety	Not measured.
11.	Delivery of intervention	Not measured.

No	Metric	Summary from evidence review
1.	Event free survival (EFS)	The event-free survival (EFS) is defined by Maury et al (2016) as a composite endpoint of failure of complete remission induction, relapse, and death. It refers not just to the patient being alive, but alive and free from relapses or treatment failure. Maury et al (2016) reported that patients who received Rituximab in addition to standard chemotherapy as first line therapy, for Ph-negative CD20 positive B-ALL, had longer EFS than those assigned to the control group. After a median follow up of 30 months, 58% of patients on Rituximab had not experienced an event compared with only 45% in the control group. The ratio of Rituximab treated patients experiencing any of these events compared with those who received standard chemotherapy (the hazard ratio) was 0.66 (95% CI, 0.45 to 0.98; p =0.04). Although no significant effect was observed of Rituximab on overall survival, it is possible that the statistically significantly higher EFS reported in this study may be meaningful to patients. However, the meaningfulness of this to patients is not clear. This result must be treated with caution because no absolute numbers were reported and hence the number of avoided events (the size of the effect on EFS) is not clear. It is also not clear how meaningful an increase in EFS is to patients compared to the reported lack of effect on overall

		survival, which may be more important to patients with a potentially fatal condition. Also, the 95% confidence interval for the hazard ratio is wide (95% confidence interval 0.45 to 0.98) and the upper limit of the confidence interval is close to 1, which indicates that it was only just statistically significant. The multiple sources of bias in the methodology employed in this study, for example higher rates of allogeneic stem cell transplantation in the Rituximab group and the lack of blinding of assessors, suggest further need for caution in interpretation of these results. This study was non-blinded, and patients were assessed by the investigator not an independent assessor.
2.	Haematological remissions after one or two induction courses	Patients are considered to be in haematological remission if they have: ≤ 5% blasts in normocellular or hypercellular marrow with absolute neutrophil count ≥ 1 x 109/L and resolution of extramedullary disease. Maury et al reported on the rate of haematological remission after one or two courses or treatment and did not find any significant benefit of Rituximab compared with standard chemotherapy in terms of remission after one or two induction courses. Maury reported complete remission rates of: Rituximab 92% versus control 90% (p = 0.63). These results suggest that most patients will respond to the initial induction chemotherapy and that the initial response does not appear to be improved or worsened by adding in Rituximab to the chemotherapy. This result is from a randomised controlled open-label study. It is not clear whether it was sufficiently powered to assess differences in this outcome measure.
3.	Early mortality during induction	Maury et al reported rates of early death during induction. This outcome was not defined, and the statistical significance was not reported. Overall there were 7 deaths during induction in the rituximab group and 9 deaths during induction in the control group (p = NR). This result does not clarify whether the addition of Rituximab to standard chemotherapy results in any benefit or harm over standard chemotherapy alone in terms of early mortality during induction. A definition of the time period covered, and statistical tests may help understand this result better, but it is also not clear whether the study was adequately powered to detect a difference in this outcome.

4.	Cumulative incidences of relapse	Maury et al reported the cumulative number of relapses experienced by these patients during the follow up period. There was a significantly lower cumulative incidence of relapse in the Rituximab group; Rituximab 21% v control 34%; HR 0.52 (95% CI, 0.31 to 0.89; p = 0.02). This means the patients are likely to experience fewer relapses if they had Rituximab added to their chemotherapy. This result should be treated with caution because it was reported by the investigators assessment, not by any objective parameters and not by an independent assessor. In addition, it did not translate into significantly longer overall survival and there were no data on quality of life changes during survival or during relapse. This means that patients are likely to have fewer relapses during their follow up period, but without any improvement in overall survival or measure of the effect of the relapse on the patients' quality of life, the clinical benefit of this reduction is relapse rate is uncertain.
5.	Cumulative incidences of death during the first remission	Maury et al reported the cumulative number of deaths in each study group during the first remission. Addition of Rituximab to standard chemotherapy did not confer any benefit over standard chemotherapy in terms of the cumulative incidences of death during the first remission; Rituximab 13% versus control 13%; HR 0.98 (95% CI, 0.45 to 2.12; p = 0.96) This means a similar proportion of patients died in each treatment group during the first remission, and addition of Rituximab did not reduce the incidence of death at this stage. However, it is not clear from the report whether the study was sufficiently powered to measure a difference in this specific outcome.
6.	Severe adverse events associated with induction, consolidation, late intensification of SCT, and maintenance	Severe adverse events associated with induction, consolidation, late intensification of chemotherapy, and maintenance were reported. According to Maury et al, the overall incidence of severe events did not differ significantly between the two groups; Rituximab 96% versus control; 92% (p = 0.72).

		Infectious events were slightly more frequent in the Rituximab group, but the difference was not significant; Rituximab 71% versus control; 55% (p = NS). Laboratory abnormalities were also not significantly different between groups; Rituximab 22% versus control; 23% (p = NS), Severe allergic events to L-asparaginase were more common in the control group than in the Rituximab group; Rituximab 2% versus control 11% (p = 0.002) These results found no increase in severe adverse events associated with the addition of Rituximab to standard chemotherapy and found a reduction in severe allergic reactions to L-asparaginase. It is not clear what the effect of this is on the reliability or interpretation of the results. This result should be treated with some caution as it was an open-label trial which means that there was no blinding regarding which treatment the patient had and there could therefore have been bias in the reporting of adverse events.
7.	Complete remission duration (CRD)	Thomas et al reported on Complete Remission Duration (CRD), which was measured from CR to relapse with a median follow-up of 64 months (range 4 to 200). When analysing the CD20-positive group, incorporation of Rituximab into the modified hyper-CVAD regimens was associated with significant improvements in 3-year CRD rates; 67% v 40% (p = 0.002). Thomas et al also carried out a subset analysis in patients aged ≤ 60 years. (n = 114). 70% of Rituximab treated patients had a 3-year CRD, with just 38% in the control group (p < 0.001). This result suggests that adding Rituximab to standard chemotherapy prolongs the period during which the patients remain in remission, and younger patients might benefit more from this treatment approach. The importance of this finding is not certain because, apart from younger patients, no improvement in overall survival was observed. In addition there were several other design flaws that could have biased the result. Importantly, there were several changes to the standard chemotherapy protocol used during the course of the study and all the Rituximab treated patients were treated under a different protocol from the control patients.

8.	Mean incremental cost-effectiveness ratio (ICER)	The incremental cost-effectiveness ratio (ICER) is used to assess the economic benefit of different health interventions. It is a ratio of the total cost of the treatment and other associated costs to the health utility benefit it is believed to provide. The latter is usually measure in life-years gained (LY). This is usually adjusted by a factor to account for changes in quality of life: quality-adjusted life years (QALY). Nam et al evaluated the cost/QALY of adding rituximab to standard chemotherapy for de novo treatment of Ph-negative CD20 positive B-ALL. Data from the Maury et al (2016) study was used for estimation of the effectiveness of the therapy. Costs were based on the Canadian healthcare systems and expert opinion. Rituximab added to standard chemotherapy led to greater total cost versus standard chemotherapy alone; difference = Canadian $48,108, 2.63 life years and 2.2 QALYs. This led to an ICER of Canadian $18,327/LY and $21,828/QALY (~£12,308 per QALY). This means that adding Rituximab to standard chemotherapy will cost approximately £12,308 for ever quality adjusted life year gained. However, this result should be treated with caution because the efficacy data is based on the Maury et al (2016) study which showed no gain in overall survival rate, so the LY and QALY gains might have been overestimated. The costs were calculated from the perspective of the Canadian publicly funded healthcare payer which does not necessarily apply in the UK Health Service where both costs and management strategies may differ. Three of the authors (including the main author) were employed by the manufacturer.

Patient Impact Summary

The condition has the following impacts on the patient's everyday life:

- **Mobility:** Patients have no to slight problems in walking about.
- **Ability to provide self-care:** Patients have slight/moderate problems in washing or dressing.
- **Undertaking usual activities:** Patients are unable to do their daily activities.
- **Experience of pain/discomfort:** Patients have no or slight pain or discomfort.

- **Experience of anxiety/depression:** Patients are moderately to severely anxious or depressed.

Further details of impact upon patients:
Acute lymphoblastic leukaemia (ALL) in adult patients is a life-threatening condition, which requires intensive and prolonged chemotherapy. Treatment may also involve an allogenic bone marrow transplant in the first year. Treatment affects the patient's quality of life dramatically for several years. Patients are unable to work and undertake usual activities and will have to protect themselves from catching infections.

Despite all these efforts the eventual outcome of the disease (in terms of prognosis) is uncertain, hence increasing patient's and carer's anxiety and depression levels. Most patients will initially respond to therapy but then subsequently relapse requiring further therapies. More than 50% of adult patients will ultimately die from the disease itself or from therapy complications.

Further details of impact upon carers:
Many of the patient's usual activities will have to be taken up by carers. The diagnosis leads often to financial hardships and significant uncertainty about the future.

Considerations from review by Rare Disease Advisory Group
Not applicable.

Pharmaceutical considerations
This clinical commissioning policy proposition recommends the addition of rituximab to first-line standard chemotherapy for CD20 positive B-cell precursor acute lymphoblastic leukaemia in adults. This is an off-label use of rituximab which is excluded from national tariff.

Considerations from review by National Programme of Care
1) The proposal received the full support of the Cancer PoC on 6th August 2020.