

Clinical effectiveness and cost-effectiveness results from the randomised, Phase IIB trial in previously untreated patients with chronic lymphocytic leukaemia to compare fludarabine, cyclophosphamide and rituximab with fludarabine, cyclophosphamide, mitoxantrone and low-dose rituximab: the Attenuated dose Rituximab with ChemoTherapy In Chronic lymphocytic leukaemia (ARCTIC) trial

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Scientific summary

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Scientific summary

Background

The conventional therapy for patients with chronic lymphocytic leukaemia (CLL) who require therapy and are considered fit for fludarabine-based treatment is the combination of fludarabine, cyclophosphamide and rituximab (FCR) (Mabthera®, Roche Products Ltd). Rituximab is a monoclonal antibody targeting the CD20 antigen, which is expressed on B-cells (both normal and malignant). CD20 is characteristically expressed at a low level in CLL. The standard dose of rituximab used in FCR for CLL (375 mg/m² in cycle 1 and 500 mg/m² in cycles 2–6) was selected based on the dose approved as a single agent in follicular lymphoma. The problem with identifying the dose of rituximab, as with many other monoclonal antibodies, is that the maximum tolerated dose is not reached in Phase I trials owing to the specificity of this type of targeted therapy. In effect, the maximum tolerated dose is governed by the volume that can be infused rather than the toxicity of the molecule. The standard dose of rituximab as a single agent in follicular lymphoma of four weekly doses of 375 mg/m² was selected pragmatically depending on the amount of available rituximab and the number of patients required in the original follicular lymphoma trial. The same dose was then used when rituximab was combined with various different chemotherapy regimes in lymphoma, with no further Phase I data to define this more accurately. The dose upon which the CLL dose was derived was 375 mg/m² but, as the expression of CD20 in CLL is characteristically lower than in the other B-cell malignancies and in normal B-cells, the rituximab dose per cycle of chemotherapy in CLL was arbitrarily increased to 500 mg/m². When higher doses of rituximab [three doses of 500 mg/m² per cycle of fludarabine and cyclophosphamide (FC) compared with a single dose, which is conventional; so-called FCR3] were used in combination with fludarabine plus cyclophosphamide in a small Phase II trial, there was no evidence that the responses were any higher. However, there is good evidence that small doses of rituximab have biological activity in CLL. Even small doses of rituximab, as low as 20 mg, lead to an immediate reduction in circulating CLL cells by the end of the infusion. This is associated with a marked reduction in the expression of CD20 on the CLL cells, which becomes apparent during the infusion. If a similar, or larger, dose of rituximab is then given on the following day there is often no further evidence of a fall in lymphocyte count owing to the lack of CD20 antigen expression on the CLL cells. There is evidence that this reduction in CD20 expression may be attributable to the ‘shaving’ of CD20 from the CLL cell. The idea behind the mechanism for CD20 shaving is that, initially, cells coated in rituximab are removed by the reticuloendothelial system, but given the large number of CLL cells, this mechanism is rapidly saturated. At this point, the rituximab bound to the CLL cells coalesces and these aggregates are removed by the reticuloendothelial system, a process called trogocytosis. Therefore, bound and unbound CD20 antigens are removed from the CLL cells, making them non-responsive to further doses of rituximab. A possible consequence of this would be that higher doses of rituximab would remain in the plasma and as soon as any CD20 antigen returns, the same mechanism of shaving would apply until the free rituximab was exhausted or excreted. At this point, CD20 expression would return, allowing further doses of rituximab to be effective. If the above is true then giving ever-increasing doses of rituximab would not be effective and, in fact, lower doses that had biological activity but did not lead to high free plasma levels might allow the more rapid return of the CD20 antigen, thereby enabling subsequent doses of rituximab to have biological activity again. This would suggest that repeated lower doses of rituximab may be equally, or even more, effective, particularly when there is a large amount of tumour antigen present (at the initiation of therapy). The cost of rituximab constitutes approximately 80% of the acquisition costs of FCR, and the infusions last several hours, creating logistic problems for both patients and hospitals. If the dose of rituximab were to be reduced by several fold, then both of these issues would be ameliorated.

Two earlier Phase II trials in both previously untreated and relapsed CLL patients have suggested that the addition of mitoxantrone to FCR results in greater efficacy and is well tolerated, although neither of the trials was randomised to validate this.

There were two key assumptions in the design of the Attenuated dose Rituximab with ChemoTherapy In CLL (ARCTIC) trial. First, it was assumed that the efficacy of a low dose of rituximab [100 mg (i.e. one vial)] was comparable to the conventional dose (500 mg/m²) when combined with combination chemotherapy in CLL. Second, it was assumed that the addition of mitoxantrone to FC would increase the response rates and be tolerable. Mitoxantrone was, therefore, added to the chemotherapy backbone of FC in order to allow for the possibility that low-dose rituximab might be inferior to the conventional dose. It would then follow that FCM-miniR should be at least non-inferior and, therefore, cost-effective when compared with FCR.

Objectives

The objective of the ARCTIC trial was to assess whether the combination of fludarabine, cyclophosphamide and mitoxantrone with a low dose of rituximab (FCM-miniR; 100 mg per cycle) was non-inferior to the conventional FCR therapy in patients with CLL requiring therapy for the first time. This included the complete remission (CR) rate as the primary end point, with important secondary end points including progression-free survival (PFS), overall survival (OS), overall response rate (ORR), eradication of minimal residual disease (MRD) following treatment, safety and toxicity, and cost-effectiveness. The objective was to use the results of ARCTIC, assuming they were positive, to help design a larger, definitive, Phase III trial.

Methods

The ARCTIC trial was a multicentre, randomised, controlled, open, Phase IIB non-inferiority trial including patients with previously untreated CLL who required treatment by International Workshop on Chronic Lymphocytic Leukaemia (IWCLL) criteria. Patients were randomised on a 1 : 1 basis to receive FCR or FCM-miniR. The intention was to include 206 patients from hospitals around the UK. The trial was monitored by an independent Data Monitoring and Ethics Committee (DMEC) and a Trial Steering Committee (TSC), and there was a pre-planned interim assessment of efficacy after 103 participants had completed therapy.

Primary end point (response assessment) data were centrally reviewed by an independent panel of CLL clinicians who determined, using IWCLL criteria, whether or not a CR had been achieved. A formal analysis of the primary end point used an adjusted logistic regression model, and time-to-event analyses were performed using adjusted Cox regression analyses. The economic evaluation used a within-trial analysis, in which cost-effectiveness was assessed within the 24-month trial period using individual patient data collected during the trial, and a decision analytic model analysis, in which cost-effectiveness was assessed over a lifetime horizon using standard modelling techniques applied to the trial data in order to extrapolate the trial results.

Results

A total of 200 of the planned 206 patients were entered into the ARCTIC trial between December 2009 and September 2012 from 34 centres across the UK. There were nine withdrawals (4.5%) during the trial, which were balanced across the treatment arms. A total of 141 participants (70.5%) completed the recommended six cycles of treatment, with slightly more in the FCR arm than the FCM-miniR arm (70.0% vs. 64.6%). The majority of participants discontinuing treatment did so because of toxicity. At the DMEC's pre-planned interim analysis, 82.9% of participants achieved a CR in the FCR arm compared with 61.4% of participants in the FCM-miniR arm. Although the difference between the two arms was not significant (at the adjusted 0.5% level) the experimental treatment had the lower CR rate. As the results were approaching significance in favour of the control group, and there was evidence of additional toxicity in the FCM-miniR arm, the trial was closed early at the recommendation of the DMEC, and participants still

receiving FCM-miniR were recommended to transfer to treatment with FCR for the remainder of their treatment cycles.

At the final analysis of the primary end point (at 3 months post treatment) 100 participants had completed FCR, 79 had completed FCM-miniR and 21 had initially received FCM-miniR but crossed over to receive FCR at some point in their treatment following the advice of the DMEC recommendation. A total of 76.1% of participants achieved a CR in the FCR arm compared with 54.7% in the FCM-miniR arm. The difference in proportions (FCM-miniR – FCR) was –21.4% [95% confidence interval (CI) –35.8% to –7.0%] and the adjusted analysis gave an odds ratio of 0.37 for the treatment effect (95% CI 0.19 to 0.73), indicating that participants in the FCM-miniR were significantly less likely to achieve a CR. Therefore, at the final analysis there is very strong evidence that FCM-miniR is not non-inferior to FCR in terms of CR rates at 3 months post treatment, and that it is, in fact, significantly inferior. The analysis of the per-protocol population and the sensitivity analyses support this conclusion.

The ORR was high at 92.6%, with 7.5% fewer participants achieving at least a partial response in the FCM-miniR arm compared with the FCR arm (95% CI –15.6% to 0.6%).

The eradication of MRD in the bone marrow at the end of therapy is a strong predictor of outcome in CLL. At 3 months post treatment, 53% of participants were MRD negative, with a higher percentage of participants in the FCR arm than the FCM-miniR arm (57.0% vs. 46.4%). The difference in proportions between FCR and FCM-miniR was not statistically significant ($\chi^2 = 1.97$; $p = 0.160$), although it was approaching significance.

There was no significant difference between the treatment arms with respect to PFS, nor was there a significant difference in OS. However, there was a non-significant trend towards the FCM-miniR participants performing worse in terms of both PFS and OS. At 24 months post randomisation, 89.4% of the FCR participants remained progression-free compared with 79.1% of the FCM-miniR participants. In terms of OS at 24 months, 95.8% of the FCR participants remained alive compared with 88.5% of the FCM-miniR participants.

In the exploratory subgroup analyses, PFS and OS were significantly improved for participants who were MRD negative or who had achieved a CR at 3 months post treatment, or who received more than three cycles of treatment. In addition, of those participants who were MRD positive, OS was worse in participants who received FCM-miniR than in those who received FCR, suggesting that after progression the participants initially treated with FCM-miniR may respond more poorly to, or be too unwell to receive, salvage therapies. Longer follow-up data are required to be able to assess reliably the time-to-event outcomes, and these will be updated in future.

More participants experienced a serious adverse event (SAE) in the FCM-miniR arm compared with the FCR arm (58.2% vs. 49.0%), as well as a serious adverse reaction (49.4% vs. 41.0%). More participants in the FCM-miniR arm were hospitalised for a SAE during the trial (51.9% vs. 46.0%) and six SAEs were deemed to be life-threatening or resulted in death compared with three in the FCR arm. A similar proportion of participants experienced an adverse event (AE) in each treatment arm, but a higher proportion of Common Terminology Criteria for Adverse Events grade 3 and 4 AEs were reported in the FCM-miniR arm (22.4% vs. 15.0%). There were no treatment-related mortalities within 3 months of completing protocol treatment.

The results of the economic analysis indicate that FCM-miniR is cost-effective in the short term, but only as a result of saving money at the expense of worse health outcomes, and is unlikely to be cost-effective in the long term. Over the 24-month trial period, FCM-miniR produced a mean cost saving of £6619 and a mean quality-adjusted life-year (QALY) loss of –0.059 compared with FCR. The incremental cost-effectiveness ratio (ICER) was £112,193, indicating that for every £112,193 saved by adopting FCM-miniR, one QALY would be lost. At a willingness-to-pay threshold of £20,000 per QALY, this leads to a net benefit gain of £5439

(equivalent to 0.27 QALYs), and there was a 100% probability that FCM-miniR is cost-effective. However, the cost-effectiveness of FCM-miniR was not sustained in the long-term analysis. Results of the decision model indicate that over a lifetime horizon, FCM-miniR produces a mean cost saving of £7723 and a mean QALY loss of -0.73. The associated ICER is £10,651, indicating that for every £10,651 saved by adopting FCM-miniR, one QALY would be lost. At a £20,000 per QALY threshold, this leads to a net loss of -£6780 (-0.34 QALYs), with a 19% chance that FCM-miniR is cost-effective.

Conclusions

Participants randomised to FCM-miniR had a significantly lower CR rate than those randomised to FCR (FCM-miniR 55% vs. FCR 76%), indicating that FCR is the more effective treatment. This seemed, at least in part, to be attributable to the higher toxicity associated with the addition of mitoxantrone to FCR. Key secondary end points also indicated that FCR had greater efficacy, with a higher proportion of participants achieving eradication of MRD (57% for FCR compared with 46% for FCM-miniR). The follow-up in the trial is still immature (median 37.3 months from randomisation) but, to date, the PFS and OS are good compared with previous studies and there is no significant difference between the two treatment arms, although there is a possible trend towards FCR patients having improved PFS and OS. The cost-effectiveness analysis indicates that, although FCM-miniR is expected to be cost-effective in the short term, it is unlikely to be cost-effective when taking into account long-term costs and health benefits.

In summary, there is strong evidence to suggest that FCM-miniR is not non-inferior to FCR in terms of CR at 3 months post treatment and that the addition of mitoxantrone adds toxicity to FCR. Although FCM-miniR was found to be cost-effective over the trial period, it is unlikely to be cost-effective in the long term. In view of this, FCM-miniR will not be taken forward into a larger, definitive, Phase III trial.

The trial demonstrated that oral FCR yields extremely high response rates compared with historical series in which the chemotherapy was given intravenously and it remains the gold-standard therapy for CLL in patients considered fit for fludarabine-based therapy.

Trial registration

The trial is registered as ISRCTN16544962.

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