Idelalisib and Rituximab in Relapsed Chronic Lymphocytic Leukaemia

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Background

Idelalisib (previously known as CAL-101, GS-1101) is the second kinase inhibitor after ibrutinibto have been extensively investigated in CLL. It is a potent, orally available, selective small-molecule inhibitor of the delta-isoform of phosphoinositide 3-kinase (PI3K). The delta isoform is one of four catalytic isoforms (p110 α, β, γ, and δ) of PI3K, that differ in their tissue expression, with PI3Kδ being highly expressed in lymphoid cells and therefore most critical for CLL. The rationale for the development of this drug for CLL is based upon the importance of B-cell receptor (BCR)-signalling in CLL-cell survival. Signalling through the BCR activates PI3K, leading to a variety of downstream events including protein kinase C activation and calcium mobilisation, which result in activation of gene expression and the promotion of cell division and cell survival. Inhibition of several of the kinases in this cascade has shown to be toxic to CLL cells, underpinning the development of several small molecule targeting kinases in this pathway as novel treatments for CLL and other B-cell malignancies.

While significant advances have been made in the treatment of CLL over the last decade, allogeneic haematopoietic stem cell transplantation remains the only curative option. Unfortunately the high rates of morbidity and mortality associated with this procedure make it unsuitable for many patients with CLL. Combination chemo-immunotherapy with fludarabine, cyclophosphamide, and rituximab (FCR) is now established as the standard of care, with overall response rates (ORR) of 95%, and complete remission (CR) rates of 44%. However this treatment is also too toxic for many elderly patients, who constitute the majority of individuals with this disease, and there remain subgroups of patients for which this therapy has minimal activity, or who relapse rapidly after treatment .Therefore there remains a critical need for novel agents. Idelalisibhas been shown to have clinically significant activity and acceptable toxicity in patients with relapsed or refractory CLL in phase I studies. This phase 3, randomized, double-blind, placebo-controlled trial investigated the combination ofidelalisib and rituximab in patients with relapsed CLL.

Summary of study

220 patients were randomised into two arms (110 patients in each arm) to receive rituximab with either idelalisib or placebo. Patients were eligibleif they had CLL that had progressed within 24 months of last treatment and were not able to receive cytotoxic agents for $\geq$1 of the following reasons: severe neutropenia or thrombocytopenia, renal failure,or a CIRS score > 6.

Characteristic	**Idelalisib + Rituximab**	**Placebo + Rituximab**
Median age	71 years	71 years
Unmutated*IGVH*	83%	85%
Del 17p or *TP53* mutation	42%	45%
Median CIRS score	8	8

Median previous Rx	3	3

Rituximab dosing: All patients were to receive8 infusions of rituximab: an initial dose 375 mg/m^2 followed by 4 doses of 500 mg/m^2 every 2 weeks; then 3 doses of 500 mg/m^2 every 4 weeks.

Idelalisib dosing: Patients were randomly assigned to receive 150mg/day idelalisib or placebo.Patients on idelalisib who progressed could have their dose increased to 300mg/day. Patients on placebo who progressed could enroll in a 2nd study to receive idelalisib.

Efficacy: The combination of rituximab and idelalisib showed a significant advantage over rituximab and placebo with an improvement in progression free survival. At 24 weeks 93% of patients in the idelalisib group had not progressed, compared to only 46% in the placebo group; with a median progression free survival of only 5.5 months in the placebo group (median PFS not reached in the idelalisib group). Disease progression occurred in only 12 patients in the idelalisib group compared to 53 patients in the placebo group. There was also a difference in overall survival with 92% of patients remaining alive at 12 months in the idelalisib group compared to only 80% in the placebo group.

In terms of response rates, the overall response rate was 81% in idelalisib group and 13% in placebo group. All responses were partial responses; there were no complete responses.All patients treated with idelalisibhad a reduction in lymph node size with 93% having a reduction in size of $\geq$50% or more compared to only 4% of patients in the placebo arm.

Importantly there were no differences in response toidelalisib and rituxmab in “high risk” patient withunmutated*IGVH* genes or del 17p/*TP53* mutations, compared to more favourable subgroups.

Adverse events: Adverse events were common with over 90% of patients having at least one adverse event. At least one serious adverse event occurred in 40% patients in the idelalisib group and 35% of patients in the placebo groups. However, rates of adverse events were consistent with those expected in an older cohort of patients with relapsed CLL that had received extensive prior therapy. The main adverse events attributable to idelalisib were elevations in aminotransferases, rash anddiarrhoea.

Discussion

One of the major limitations of this study is the short duration of follow-up with recruitment having only ended in August 2013. This was due to the data and safety monitoring board halting the study at the first interim analysis due to the large differences in overall response rates and the short progression free survival in the placebo group. This means that this study gives very little information on the medium to long-term durability of response to idelalisib and rituximab. Irrespective of this, this study did show significant improvements in both progression free and overall survival despite the short follow-up. It will be interesting to see how these patient cohorts do over the longer term.

Unusually for a phase 3 trial, the age and degree of co-morbidities of the patient groups reflect the actual experience in the clinic. The median age of patients in this study was 71 years, and the patient population included a significant proportion of patients with poor risk disease, with over 80% of patients having unmutated*IGVH* genes and over 40% of patients having deletion of 17p/*TP53* mutations. The authors highlighted the observation that the idelalisibwas equally effective in patients with these unfavourable features, although it could be argued that all patients in this study had “poor risk” disease due to their clinical phenotype, irrespective of the presence/absence of standard biological prognostic markers. Furthermore, the short duration of follow-up means that this interpretation may be rather premature, given that in ibrutinib studies (Byrd et al. NEJM 2013) patients with deletions of 17p or 11q are already starting to show increased rates of disease progression.

Despite this, the improved efficacy on a background good tolerability mean that idelalisib does represent a significant step forward for the treatment of CLL. Idelalisib was relatively well tolerated in this study in a frail elderly population of patients with no significant increase insevere side effects over rituximab monotherapy. Many of the existing chemotherapeutic treatments exacerbate the existing immune-suppressed state found in these patients, making them challenging to treat. This is less of a problem with idelalisib and ibrutinib, meaning that these agents represent good therapeutic option for these individuals. However, one of the major concerns is the lack of complete responses (CRs). No CRs were seen in this study; similarly only a small minority of patients have been achieving CRs in studies with ibrutinib (Byrd et al, NEJM 2013). Add this issue to lack of data on durability of responses, and it becomes unclear whether younger fitter patients will derive the same degree of benefit from these agents. Long-term follow-up of patients treated with FCR has raised the issue of whether the proportion of patients who remain in CR for several years after treatment are actually “cured”. Therefore fitter patients (“go-go”) who are able to tolerate FCR may still be better off receiving it,whereas patients with co-morbidities(“slow-go” or “no-go”) may be the ones who derive most benefit from novel agents such as idelalisib or ibrutinib. However, many further questions need to be addressed: particularly the efficacy of idelalisib in the treatment naïve setting. Preliminary data from a phase II study (O’Brien et al. ASCO 2013 Abstract 7005) has suggested that the combination of idelalisib and rituximab upfront is highly effective in a cohort of older patients (median age 71), with an ORR of 96% and no on-study relapses.

One of the biggest challenges to the use of idelalisib in the UK will be the cost of this drug and it is not clear how NICE will deal with this. A related issue is how long patients should receive this agent for. As with ibrutinib, current trials with idelalisib have allowed continuation of therapy until progression. At the termination of this study 81% of patients in the idelalisib group were still receiving the drug. It remains unclear whether it is safe for patients to receive idelalisib long-term, and also whether there is a rationale to stop this agent in patients who are in complete remission. Much further work needs to be

done in this area and it is likely that MRD monitoring will have role to play, but it is also probable that cost implications will also have to be taken into account.

Reviewed by John Riches; March 2014