Lenalidomide maintenance treatment after imatinib discontinuation: results of a phase 1 clinical trial in chronic myeloid leukaemia

Treatment-free remission (TFR) is achieved by 40–60% of chronic myeloid leukaemia (CML) patients who stop imatinib treatment after a sustained BCR-ABL1 level ≤0.0032% (MR4.5) (Ross et al, 2018; Saussele et al, 2018). Patients who need to restart imatinib typically regain MR4.5 within 3 months, but may need to remain on treatment indefinitely. There are limited data on the outcomes of a second TFR attempt (TFR2) (Legros et al, 2017; Ross et al, 2018).

References


Evidence from several studies suggests that immunological factors, particularly increased numbers of natural killer (NK) cells, may influence TFR outcomes (Imagawa et al, 2015; llander et al, 2017; Rea et al, 2017). Lenalidomide increases T- and NK-cell proliferation and activation, and enhances NK cytotoxicity (Davies et al, 2001). It is widely used for the treatment of myeloma, but is not approved for CML. We designed a Phase 1b clinical trial (‘LENI’; ACTRN12615001169538) for patients planning a TFR2 attempt using lenalidomide to augment immune function.

This single centre non-randomized clinical trial was planned to enrol 20 CML patients in MR4.5 for ≥12 months on imatinib after previously having failed a TFR attempt. In the combination phase of the study, patients continued imatinib at the previously established dose and added lenalidomide 5 mg daily for 1 month, with escalation as tolerated to 10 mg daily for a further 5 months. If patients maintained MR4.5, imatinib was discontinued and lenalidomide maintenance treatment was continued for 6 months. Aspirin was used as thromboprophylaxis, following standard practice when lenalidomide is used for myeloma. Lenalidomide could be stopped earlier, and imatinib restarted, in the event of loss of major molecular response (loss of MMR; BCR-ABL1 >0.1%).

Real-time quantitative reverse transcription polymerase chain reaction (RQ-PCR) monitoring was performed every 3 months during the combination phase, and monthly for 12 months after stopping imatinib together with highly sensitive, patient-specific BCR-ABL1 DNA PCR.(Ross et al, 2010, 2018) Immunological studies were planned at baseline, 3 and 6 months during the combination phase, at 3 and 6 months during the lenalidomide maintenance phase, and at 3, 6 and 12 months after stopping lenalidomide.(Hughes et al, 2017) The primary endpoint was the safety of lenalidomide in combination with imatinib.

The study was closed prematurely on the recommendation of the safety monitoring committee after only 3 patients were enrolled (Table 1), all of whom had previously participated in the Australasian Leukaemia and Lymphoma Group CML8 (TWISTER) study.(Ross et al, 2018) All patients had MR4.5 and undetectable BCR-ABL1 mRNA at study entry (UMRD4.5). Patient 2 remained on lenalidomide 5 mg daily due to cytopenia during the first month of the combination phase. The other patients completed the combination phase at the planned lenalidomide dose of 10 mg daily. Patient 1 developed unprovoked pulmonary embolism 4 months after stopping imatinib, while on lenalidomide maintenance. Patient 2 developed right optic neuritis, presumed ischaemic, 3 weeks after stopping imatinib while on lenalidomide maintenance therapy, which was then stopped. Eight weeks later she developed pulmonary embolism. Patient 3 was then taken off lenalidomide maintenance pre-emptively. The only other adverse event of grade 2+ occurring in >1 patient was neutropenia. Following the discontinuation of lenalidomide there were two further serious adverse events: oesophageal bleeding whilst on anticoagulation (Patient 3) and squamous cell carcinoma of the skin 10 months after lenalidomide was stopped (Patient 2).

All 3 patients remained in continuous UMRD4.5 at last follow-up 20–26 months after stopping imatinib (Fig 1). In the French RE-STIM study, in which patients stopped imatinib for a second time without additional treatment, 12/45 patients maintained MR4.5 (27%), and loss of UMRD4.5 within 3 months at the first TFR attempt (TFR1) was significantly associated with a higher risk of failure at TFR2 (hazard ratio: 2.0).(Legros et al, 2017) Our patients had molecular relapse characteristics at TFR1 that were comparable to those of the RE-STIM patients: the two patients who did not lose MMR had a significant increase in BCR-ABL1 mRNA within the first 4 months. However, our patients also had an exceptionally long duration of UMRD4.5 after TFR1 (versus a median of 24-5 months in RE-STIM), and duration of deep molecular response may itself affect the probability of successful tyrosine kinase inhibitor (TKI) discontinuation (Saussele et al, 2018).

The combination of imatinib and low dose lenalidomide was well-tolerated, with no unexpected toxicity, but lenalidomide maintenance after stopping imatinib was associated with thrombotic adverse events in the first two patients, leading to closure of the study. No clinical trial to date has reported a significantly increased rate of thrombotic events following imatinib discontinuation. There has been no prior study using lenalidomide in CML, and both the primary safety endpoint and the protocol-defined stopping rules in LERI referred only to adverse events during the combination phase. When designing the study, we based our estimate of thrombosis risk on data from patients with del(5q) myelodysplastic syndrome, because this is also a myeloid malignancy, treated with a similar lenalidomide dose, and typically not combined with corticosteroids or other cytotoxic therapy. In a clinical trial involving 103 patients on lenalidomide 10 mg daily for a median of 2 years, there were three occurrences of deep vein thrombosis.(List et al, 2006) The timing of the events in the LERI study raises the possibility that imatinib discontinuation and concomitant lenalidomide treatment interacted to potentiate the

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<th>Table I. Patient characteristics at study entry.</th>
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CML, chronic myeloid leukaemia; MR4.5, deep molecular response (BCR-ABL1 level ≤0.0032%); TFR1, first attempt at first tyrosine kinase inhibitor discontinuation.
thrombotic risk. It is possible that imatinib has an anti-thrombotic effect that is lost on discontinuation, or that imatinib withdrawal leads to a pro-inflammatory, prothrombotic state.

Lenalidomide did not reduce the level of BCR-ABL1 (by DNA PCR), but was associated with an increase in markers of immunological reactivity (Fig 1). Most of these changes were transient and reverted by the end of the combination phase. All three patients remained in TFR at last follow-up, but the small number of patients enrolled precludes any definitive assessment of the efficacy of this approach. An immunomodulatory strategy might be worthy of further investigation if the safety concerns can be addressed by changes to the sequence of imatinib/lenalidomide discontinuation, more effective thromboprophylaxis, or the use of an alternative immunomodulator. Most importantly, our experience highlights the necessity for any TFR clinical trial involving novel treatment to balance the risk of the novel intervention against the potential benefits of TFR, and to incorporate careful monitoring for adverse events both during treatment and after TKI discontinuation.

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Author contributions

DMR designed the study and wrote the paper; ISP and YDI performed research and wrote the paper; JC, TL, PD, JM, VAS, and LC performed research; JR, DSR, DLW, SB, TPH, and ASMY designed the study and wrote the paper.

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Novel ADA2 mutation presenting with neutropenia, lymphopenia and bone marrow failure in patients with deficiency in adenosine deaminase 2 (DADA2)

We evaluated deficiency of adenosine deaminase 2 (DADA2) in a non-consanguineous family with four children (Fig 1A). Both parents and their son are unaffected. The father has panlymphopenia but is clinically well. The eldest sibling, 4 years older than the proband, had bilateral renal dysplasia and died following a myocardial infarction aged 8 years.

The proband, a 45-year-old woman, presented with recurrent upper respiratory tract infections at the age of 13 years. Subsequently, she developed persistent moderate neutropenia. From the age of 24 years, she had recurrent episodes of fever with no identifiable pathogens. Aged 44 years, she was diagnosed with panhypogammaglobulinemia, neutropenia, panlymphopenia, mild thrombocytopenia and mild bone marrow hypocellularity. She declined immunoglobulin replacement as she had minimal infections. She responded to granulocyte colony-stimulating factor (GCSF) treatment for neutropenia. The proband’s sister, who is 7 years younger, presented with shingles at the age of 11 years. She experienced recurrent upper respiratory tract infections and was diagnosed with moderate neutropenia aged 20 years. She had recurrent bouts of fever with persistent severe neutropenia and a mildly hypocellular bone marrow aspirate from the age of 35 years. Occasionally, Escherichia coli was cultured and she was treated with intravenous antibiotics. Unlike the proband, she had no response to GCSF but received antibiotic, antifungal and antiviral prophylaxis. Aged 36 years, her IgA and IgM levels were low with panlymphopenia. She had poor responses to pneumococcal vaccination. At the age of 38 years, she commenced immunoglobulin replacement due to ongoing infections despite anti-microbial prophylaxis. Salient clinical features and laboratory findings of the patients are summarised in Table I.