HAEMATOLOGICAL CANCER REPOSITIONED TO ATTACK CML CELLS

BCR–ABL1 tyrosine kinase inhibitors (TKIs) enable effective long-term management of chronic myeloid leukaemia (CML). However, complete molecular responses (CMRs)—when the CML *BCR–ABL1* molecular signature is undetectable—are rare; in patients without a CMR, relapse is common when TKIs are stopped. Now, Prost *et al.* have shown that antidiabetic PPAR γ agonists can invoke sustained CMRs in patients without a CMR to the TKI imatinib.

“Pioglitazone and other PPAR γ agonists can progressively erode the pool of quiescent CML stem cells, which are responsible for residual disease during continuous TKI therapy and relapse when TKIs are interrupted,” explains Philippe Leboulch, who co-led the study. Analyses in CML cells showed that pioglitazone synergizes with imatinib: imatinib effectively depletes proliferating CML cells only, while pioglitazone causes resistant CML stem cells to exit quiescence, sensitizing them to the TKI. Mechanistically, PPAR γ agonism downregulated STAT5 and its targets HIF2 α and CITED2 (a regulator of haematopoietic-stem-cell quiescence), which were overexpressed in CML stem cells.

Repositioning of this antidiabetic agent was investigated in three patients without a CMR after 4–6 years of imatinib therapy—two with diabetes and CML, and one with CML only. Within 6–12 months of combined pioglitazone and imatinib treatment, all patients achieved persistent CMRs for >32 months. In one patient, the CMR is ongoing after 56 months, >53 months after withdrawal of pioglitazone. Another patient has had a CMR for >38 months, without pioglitazone and imatinib for 28 months and 6 months, respectively.

The investigators are evaluating the CMR-conversion efficacy of the imatinib–pioglitazone combination in a phase II trial (ACTIM, EudraCT); interim results for 24 patients, after only 3–12 months of therapy, revealed a CMR-conversion rate of 57% (versus 27% in an historical imatinib-only cohort). “A larger phase II trial (with 80 patients) is also underway, with our colleague clinician Philippe Rousselot, to confirm and further define efficacy.”

Leboulch concludes: “we envisage that this combination will be used in an effort to eradicate CML, and hope for additional applications of this principle in other leukaemias and certain solid tumours.”

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Original article Prost, S. *et al.* Erosion of the chronic myeloid leukaemia stem cell pool by PPAR γ agonists. *Nature* doi:10.1038/nature15248