Variation in cladribine-induced lymphocyte depletion

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Introduction

Cladribine is a nucleoside analogue approved for use in active relapsing multiple sclerosis (MS). Cladribine is converted into toxic metabolites via a rate-limiting phosphorylation step catalysed by deoxycytidine kinase (dCK). Lymphocytes express high levels of dCK, rendering them especially vulnerable to cladribine-mediated cytotoxicity.

Cladribine induces depletion of lymphocytes followed by repopulation, pending cell type, over weeks-months. Analysis of pharmacokinetics of cladribine indicates there is substantial inter-individual variability in drug plasma levels. Variability in metabolic enzyme activity may impact further on heterogeneous lymphocyte depletion and repopulation kinetics . We aimed to analyse variability of lymphocyte depletion in trial and real-world cohorts treated with oral cladribine.

Methods

Data was taken from the CLARITY trial and was also collected on all people with MS (pwMS) who received oral cladribine for MS between January 2018 and July 2019 at our centre. Lymphocyte counts were measured before treatment, and at 3 months in the real-world cohort and 13 weeks in the CLARITY cohort. This service evaluation was registered with the Barts Health Clinical Effectiveness Unit (registration number: 10596).

Results

The mean absolute reduction in lymphocyte count was $0.96 \pm 0.52 \times 10^{-9}$/L (n=37) and $0.81 \pm 0.56 \times 10^{-9}$/L (n=101) in the real-world and CLARITY cohort respectively. Mean relative reduction was 46.61% ±22.19% and 42.58% ±23.32% in the real-world and CLARITY cohort respectively. Nobody in the real-world cohort had Grade 4 lymphopenia.

Discussion

This data shows that there is significant variability in lymphocyte depletion among pwMS following cladribine administration. The magnitude and kinetics of lymphocyte depletion did not differ substantially between trial and real-world cohorts. Severe lymphopenia was rare in the trial and real-world cohort and some people were noted to have only mild lymphocyte reduction. Understanding the factors that explain this inter-individual variability is an important step towards personalised treatment.