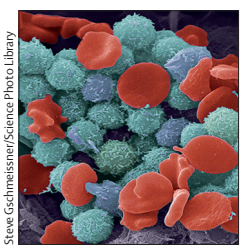
# Refining prognosis after first-line fludarabine, cyclophosphamide, and rituximab chemoimmunotherapy in chronic lymphocytic leukaemia



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One of the typical features of chronic lymphocytic leukaemia is the extraordinary heterogeneity of prognosis; overall survival can range from less than 2 years to several decades.[1,2] It has been exactly 20 years since two seminal publications showed the principal importance of *IGHV* mutation status in chronic lymphocytic leukaemia: patients with mutated *IGHV* (ie, ≥2% difference from the corresponding germline) typically have an indolent disease course and much longer overall survival than those with an unmutated gene.[3,4] In addition, younger and fit patients with chronic lymphocytic leukaemia treated with intensive first-line chemoimmunotherapy consisting of fludarabine, cyclophosphamide, and rituximab (FCR) can achieve long-lasting remissions if they have a mutated *IGHV* status.[5,6]

In *The Lancet Oncology*, Carmen Herling and colleagues[7] present their results of a retrospective study aiming to identify a gene signature model predicting a favourable outcome in *IGHV*-unmutated patients treated with first-line FCR. The study population included a training set of 101 patients treated at the MD Anderson Cancer Center (Houston, TX, USA) and a validation set of 109 patients from the FCR treatment group of the German Chronic Lymphocytic Leukaemia Study Group CLL8 trial. Using transcriptional profiling and subsequent thorough statistical analysis, the authors discovered a set of 17 genes related mainly to the metabolic activity of chronic lymphocytic leukaemia cells (genes linked with oxidative phosphorylation and purine analogue metabolism) that was associated with a significantly increased risk of disease progression: hazard ratio 3·83 (95% CI 1·94–7·59; p<0·0001) in the training set and 1·90 (1·18–3·06; p=0·008) in the validation set. The findings of this study represent an important contribution to the field of predictive markers in chronic lymphocytic leukaemia, as it shows for the first time the possibility to distinguish a subgroup of patients who are likely to achieve a relatively long remission after first-line FCR therapy despite having an unmutated *IGHV* gene.

Some experts have suggested that chemoimmunotherapy is no longer a viable option in treating those with chronic lymphocytic leukaemia because of the results of studies showing superior efficacy of the BTK inhibitor ibrutinib with or without rituximab in comparison with chemoimmunotherapy, such as FCR or bendamustine and rituximab.[8,9] However, ibrutinib treatment is associated with some disadvantages: it requires long-term administration until progression; it might be complicated by clinically significant adverse events such as bleeding or atrial fibrillation;[10] and, it might be associated with other important factors such as the development of treatment resistance, poor patient compliance to therapy, and substantial financial toxicity. Thus, time-limited chemoimmunotherapy with FCR might still be a suitable first-line option for carefully selected subgroups of patients with chronic lymphocytic leukaemia, such as those with an *IGHV*-mutated status and, possibly on the basis of the study by Herling and colleagues,[7] even some patients with unmutated *IGHV* but a favourable gene profile.

A clear and growing trend towards a patient-specific treatment approach in chronic lymphocytic leukaemia is emerging—both from the viewpoint of patient characteristics (eg, avoiding fludarabine-based treatment in patients with advanced age or substantial comorbidities, or both) as well as on the basis of features related to chronic lymphocytic leukaemia (eg, avoiding chemoimmunotherapy in patients with a mutation or deletion of the *TP53* gene). Therefore, the present study[7] deals with a very up-to-date topic. However, limitations of the study include selection bias (patient samples were selected on the basis of their availability), a relatively small number of patient samples, differences in the disease characteristics between the training and validation sets (especially the proportion of patients with advanced clinical stages and unfavourable cytogenetics), and its retrospective study design. Although the results achieved by Herling and colleagues cannot yet be translated into routine clinical practice, they are very important because they help to pave the way

towards a more personalised therapeutic approach for patients with chronic lymphocytic leukaemia. Further research in this field, preferably a large prospective, randomised trial (as also suggested by the authors of the study), would be highly beneficial in order to validate the abovementioned promising findings.

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# CDK4/6 inhibitors in breast cancer: a role in triple-negative disease?

Pharmacological inhibitors of cyclin-dependent kinases 4 and 6 (CDK4/6) were developed on the premise that they would inhibit the proliferation of cancer cells by arresting them in the G1 phase of the cell cycle.[1] Consistent with this idea, CDK4/6 inhibitors have proven to be highly efficacious in the treatment of metastatic hormone receptor-positive breast cancers, most of which depend on the cyclin D-CDK4/6–retinoblastoma protein axis for sustained cancer cell proliferation.[2,3] By contrast, the use of CDK4/6 inhibitors in triple-negative breast cancers, a group of tumours that frequently shows genomic or functional loss of retinoblastoma protein has received considerably less enthusiasm.[4]

In this context, Antoinette Tan and colleagues' Article in *The Lancet Oncology* is intriguing.[5] The authors enrolled patients with metastatic triple-negative breast cancer to a three-arm, randomised, phase 2 trial. Patients in the control group (group 1) received conventional chemotherapy (intravenous carboplatin and gemcitabine), and those in the two experimental groups received the same chemotherapy plus trilaciclib (a selective, intravenously administered CDK4/6 inhibitor), given either as a single dose before each chemotherapy infusion (group 2) or on the day before and day of each chemotherapy infusion (group 3). Surprisingly, overall survival for patients in the trilaciclib groups was significantly longer than for those in the control group.

Before unpacking the results of this trial, we must understand the rationale for undertaking it in the first place. This understanding is especially important because of concerns that by inducing G1 arrest in tumour cells CDK4/6 inhibitors can antagonise the effect of chemotherapies that typically exert their effects in the S, G2, or M phases. The investigators of this study did not appear to deem this effect to be a problem for this particular trial, presumably because of the high frequency of functional retinoblastoma protein deficiency in triple-negative breast cancers; instead, their intention was to take advantage of this antagonism in haemopoietic cells—inducing G1 arrest in bone marrow progenitors to protect them from the cytotoxic effects of chemotherapy. Indeed, the primary objective of the trial was actually to determine whether trilaciclib reduced chemotherapy-related neutropoenia. The concept is supported by previous observations that trilaciclib induces G1 arrest in haemopoietic


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