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# Laying siege to chemoresistance

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To date, tests have only been carried out on cells, but a piece of research conducted by the Department of Genetics at the UPV/EHU's Faculty of Medicine in collaboration with MD Anderson and the CNIO is opening up the door for the treatment of lymphoma types that have a lower survival rate. The study of the molecular characteristics of the tumours would enable molecules that are altered in a specific way to be identified and turned into new therapeutic targets that would improve the prognosis of patients with chemoresistant lymphomata.

But there is still a long way to go. The experimental work has been done on cells. Not on mice, let alone on humans. However, a joint piece of research between the UPV/EHU-University of the Basque Country, the MD Anderson Cancer Center Madrid —the Spanish subsidiary of the MD Anderson Cancer Center of Houston (Texas)—, and the National Centre for Oncological Research (CNIO) is suggesting that the study of gene expression in chemoresistant lymphomata could help to identify possible therapeutic targets and open up new channels of treatment.

There are still some lymphoproliferative diseases with limited therapeutic options, mainly due to the absence of targeted therapies. So although the classical Hodgkin lymphoma (HL) responds to conventional therapy based on anthracyclines (of the ABVD type) in 70 – 80 % of cases, there is a group of patients who fail to respond, and 30 % succumb to this disease. On the other hand, peripheral T-cell lymphomata (PTCL) make up a heterogeneous and highly aggressive group for which there is currently no effective therapy. These patients are also treated with therapies based on anthracyclines (of the CHOP

type), but their response is very poor: global survival depends on the PTCL subtype, but on average 70% of these patients die. So what is needed are studies that identify new therapeutic targets in refractory HL and PTCL to improve the prognosis of these patients with chemoresistant lymphomata.

So this project sought to detect the alterations that take place in these tumours and which could be targeted by drugs. The thesis "New potential therapeutic targets in conventional therapy-resistant lymphomata" (Potenciales nuevas dianas terapéuticas en linfomas resistentes a la terapia convencional), read by Esperanza Martin recently and co-supervised by África García-Orad, tenured lecturer in genetics of the UPV/EHU, and Juan Fernando García, Head of Research at MD Anderson, has submitted the initial conclusions of this research.

In each cancer alterations take place in the genes, in their structure or in their regulation. These variations are translated into modifications in the structure of specific proteins or in their quantity. These specific changes in the proteins of a specific cancer type are known as its molecular signature. Once the specific mutation of the disease or its molecular signature has been identified, a specific drug to fight these alterations can be designed. The first in this type of treatments was Imatinib. This drug is used to combat chronic myeloid leukaemia: it blocks the active centre of a protein, the kinase, the structure of which has been altered and which causes the excessive activation of the cell cycle. In the case of chemoresistant HL, histone deacetylase inhibitors (HDACi) have been identified as agents that could reverse this molecular signature. What is more, the researchers have discovered that by focussing on other molecular alterations, the effect would be boosted, thereby making it possible to determine which combination is the most suitable to treat these kinds of lymphomata that are resistant to conventional chemotherapy.

## Towards personalised medicine

Although still in an experimental phase, the preliminary results of this study constitute another step forward in the field of personalised medicine. The main aim of pharmacogenetics and pharmacogenomics is to optimize the treatment of diseases on an individual level and move towards safer and more efficient personalised therapy. The recent advances in genetics and molecular biology have expanded knowledge about the biology of some tumour types enormously; this has made it possible to improve the therapeutic possibilities and expectations of these patients, a case in point has been Imatinib in chronic myeloid leukaemia, one of the first examples of drugs designed on the basis of genetic studies. Another example of the advances in the effectiveness of personalised treatment is breast cancer. The detection of the genetic alteration responsible for the overexpression of the epidermal 2 growth factor, present in 20% of the cases diagnosed, makes it possible already to prescribe a specific treatment.

Pharmacogenetics and pharmacogenomics could provide knowledge to select those patients who are going to respond to treatment; this would enable the most suitable medication and/or the most appropriate dose for each patient to be selected. In other words, selecting the right drug and the right dose for each patient.

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