REPORT
25th SOCIAL RETURN OF THE RESEARCH
CANCER

RESISTANCE MECHANISMS TO MOLECULAR THERAPIES IN MANTLE CELL LYMPHOMA (RESTMCL)

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1. Project Summary

Mantle cell lymphoma is a rare but very aggressive disease in most patients and with limited results with current chemotherapy treatments. Mantle cell lymphoma is very heterogeneous clinically, both in response to therapy and duration of response. Patient survival has improved from less than 4 to more than 6 years in recent decades, but it is still a difficult tumor to treat, especially due to its frequent relapses. because it becomes resistant to treatments. Lately, a drug administered orally (immunotherapy), ibrutinib, has shown very good efficacy in treating relapsed mantle cell lymphoma; however, there are patients who are refractory to treatment and do not respond and other patients progress after several months/years of treatment and become insensitive to the drug. Tumor heterogeneity is considered the main determining factor of response to treatments, but its molecular bases are still not known.

We plan to carry out extensive genomic and transcriptomic studies in two series of mantle cell lymphoma cases from two ongoing clinical trials treated with ibrutinib, and to develop predictive models based on the molecular characterization of the biological variables that determine tumor heterogeneity and its impact on the evolution of the disease, resistance and susceptibility to new targeted therapies.

2. Results

From a clinical point of view, in the clinical trial of indolent mantle cell lymphoma (50 cases) we have seen that treatment with ibrutinib+rituximab, which is a chemotherapy-free option, is very safe and effective, with responses that are well sustained over time, and that ibrutinib treatment can be discontinued in those cases that have more than two years of follow-up and are disease-free.

Sanger sequencing and next-generation sequencing (NGS) are suitable technologies for identifying clonal rearrangements of the IGH gene in mantle cell lymphoma and both provide almost identical results for monitoring minimal residual disease. However, samples with low tumor infiltration rates or a high polyclonal background (corresponding to non-malignant B cells) may be better characterized by NGS, which identifies >95% clonotypic rearrangements. In cases with inconclusive results obtained

after initial testing by Sanger sequencing, NGS can be used as an additional tool to recover clonal markers.

The use of minimal residual disease quantification using very sensitive methods (next-generation sequencing) is crucial when guiding therapy, and will be very useful in stopping treatment only in those cases with a metabolic response and undetectable disease (minimal residual disease-negative), and that lack the *TP53* gene mutation.

From a biological point of view, we have seen that one of the molecular subgroups, conventional mantle cell lymphoma, initially presents a higher genetic complexity, more altered drivers, and a greater number of cases that progress clinically. Until now, we have not detected mutations in resistance genes to targeted treatments (such as ibrutinib), but we have seen that cases that progress have an evolution of clones with different alterations and already present greater genetic complexity at diagnosis.

From a clinical point of view in the clinical trial (900 patients) of the combination of ibrutinib in the first line (both in induction and during maintenance) together with or as a substitute for autologous transplant in young mantle cell lymphoma patients receiving intensive chemotherapy, it is effective and safe even in patients with high-risk characteristics such as patients who have overexpression of p53 or high proliferation of tumor cells.

3. Relevance to possible future implications

Next-generation sequencing technologies to measure minimal residual disease have yet to be implemented into clinical routine. The present work represents an initial step that, without a doubt, will favor its inclusion in more clinical trials to establish strict criteria for its application and interpretation.

When we have the final genomic results from the two clinical trials we will be able to predict more accurately the response to specific treatments, such as ibrutinib, providing insight into the optimal way to stratify patients and select the appropriate strategy for treatment to improve the survival of patients with mantle cell lymphoma.

At the moment, we have an effective and safe treatment for indolent forms of mantle cell lymphoma, which is the free combination of chemotherapy, with ibrutinib and rituximab. Until now, some of these patients were not treated, and were under observation until symptoms appeared and they had treatment criteria; sometimes starting treatment at this point was already too late; in other cases, which display indolent characteristics, the patients were intensively (over)treated, and with all the negative effects, taking into account that the majority are elderly people.

On the other hand, in aggressive forms of MCL clinical practice is now changing and ibrutinib (or similar) can be given in the first line and not only in the context of relapses. Treatment with ibrutinib in induction and maintenance together with chemotherapy is as effective as or more effective than autologous transplantation, which may also present other complications.

The new knowledge will be beneficial to practitioners as well as policy makers and other decision makers, as it will affect the design of new clinical trials and the stratification of patients with MCL prior to entry into clinical trials with clear benefits for patients.

The new knowledge can lead to the improvement of health treatments with the modification of clinical trials based on the molecular characteristics of the patients (subtype, mutations responsible for aggressiveness or resistance to treatment), it will also improve the diagnosis that will allow assigning patients with minimal residual disease in the two molecular subgroups (conventional or non-nodal leukemic), and the measurement of minimal residual disease will also have implications in clinical practice and the resulting economic costs (reduction or interruption of treatment in patients with minimal residual disease-negative mantle cell lymphoma for a sustained period and without predisposing mutations related to relapse).

Other impacts achieved are both academic and professional (training young researchers and doctors) and social (with talks aimed at the public to learn about the type of research carried out). This represents a solid basis to progressively use these data not only to increase academic knowledge of the disease, but also to make real-life decisions.

Thanks to the La Marató de TV3 project we have obtained additional funding to carry out the genetic, transcriptomic and functional characterization of samples from the TRIANGLE clinical trial, achieving a highly competitive international project (only two in the world):

Leukemia & Lymphoma Society, Ref: MCL7005-24, 2023-2027 (3.000.000$), MULTIlayer Predictive models for relapsed MCL after ibrutinib as first line therapy (MULTIPLY). PI: M Dreyling, M Ladetto & S Beà

We have also secured funding for a second indolent MCL trial, with pirtobrutinib instead of ibrutinib:

Protocol code IMCL-2023. International multicentre phase II trial to evaluate the efficacy and safety of pirtobrutinib in combination with rituximab in patients with indolent clinical forms of Mantle Cell Lymphoma. Clinical Phase II. Sponsor Grupo Español de Linfomas y Trasplante Autólogo de Médula Ósea (GELTAMO) PI: Eva Giné, responsible for the genetic characterization: Sílvia Beà. Amount awarded €1,300,000. starting 2024.

Also, we have secured funding to extend the follow-up period of the IMCL-15 trial to 12 years. The treatment has been so effective that relapses are late (12 of the 50 cases have relapsed so far), and the most important part of the project was to study the genetic changes in relapses, including functional assays.

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