Habilitation Thesis - Abstract

Prognostic Stratification in Malignan Hematological Disorders - The Step Towards Personalized Therapy

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During my 17 year activity within the *Carol Davila* University of Medicine and Pharmacy, I followed the principle that clinical and teaching activities should be integrated with laboratory activity, especially in Hematology. Thus by choosing Hematology, as a resident I oriented myself towards the analyses of blood cells by flow cytometry, in a time when this method was at its beginnings in Romania, especially for clinical diagnosis.

My teaching career starded in **february 2000,** when I was appointed as **assistant professor** following a competition – pozition 6, Hematology Department – *Colţea* Clinical Hospital, after which I continued my activity uninterrupted. From 2005 I was assigned to the Hematology Department, University Emergency Hospital Bucharest (UEHB), where in 2007 I obtained the Lecture position in 2007, and then of Associtae Professor in 2013.

Considering my current position within the new strucutre of the C*arol Davila* University of Medicine and Pharmacy, as a member of the 8th Department. which hists the Hematology, Oncology and Radiotherapy specialties, I hold that the current and future activities permit the integration in the new structure, even opening collaboration activities regarding the access to new imaging diagnostics techniques (radiology), laboratory techniques, immunophenotyping and imaging (Hematology and Oncology) and also towards the success of treatment opportunities based on molecular and immune techniques (Hematology and Oncology) and by physics techniques (Radiotherapy).

With regard to my Habilitation Thesis, it is related to my Doctoral Thesis C*HRONIC LIMPHOPROLIFERATIVE DISORDERS WITH CD5 POSITIVE B LYMPHOCYTE, IMMUNOPHENOTYPICAL AND MOLECULAR VARIABLE EXPRESSION;* sustained in May 2007, but also with my postdoctoral activity as member in the working group on CLL within the European Leukemia Net.

From 2005 I continued my doctoral research activity at the University Emergency Hospital Bucharest through implementation of immunophenotypical methods in CLL and I introduced the usage of immunophenotypical prognostic marker CD38 and ZAP-70 in the analyses of Romanian cases. Through my doctoral thesis I defined the importance of immunophenotypical markers and

elaborated immunophenotyping diagnostic strategies for routine practice. These results were disseminated as oral and poster presentations in national and international congresses.

My involvement in European organization culminated with my admittance in the European Leukemia Net, in which I have activated since 2004 as member in the CML work-group (WP4), and further in the CLL work-group (WP7) and diagnostic work-group (WP10). The WP7 activities permitted me to continue my research activities and to further improve the diagnostic and management of Romanian patients with CLL by continuing, in the spirit of my PhD thesis, prognostic marker implementation in CLL by flow cytometry and also through the IGHV (immunoglobulin heavy chain variable region) mutational status analyses, within a PNCD-1 project, and as the UEHB Project Manager I initiated the development of these techniques in Romania.

In the same spirit, I initiated the formation of the Romanian Initiative Group in the Diagnosis of CLL within the Romanian Society for Hematology – in 2009, the objectives of which are the establishment of a Romanian-CLL Patient Registry, which will permit the characterization of patient specific to this region of Europe. In 2011 we published a first Romanian CLL registry abstract at the European Hematology Association Congress – London, and in 2016 we presented at the Romanian Society for Hematology Congress a poster with the Romanian CLL pilot-registry.

At the same time, we developed diagnostic techniques by immunophenotyping in acute leukemias and implemented and coordinated the diagnostic program of acute leukemia in SUUB, we developed platelet analysis in various pathologies and thus contributed to the development of research projects that were followed by the publication has numerous articles including ISI quoted.

Perspective Projects

1. Personalized medicine in hematology-oncology: Application of molecular genetics and cytometry techniques for the prognostic evaluation of patients with CLL

Through this project I propose the implementation of routine molecular diagnostic in patients with CLL, including TP53 analyses by molecular cytogenetics and molecular biology, but also the clonality analyses b IGHV mutation analyses.

The proposed activities will be run in accordance and guidance of ERIC (European Research Initiative on CLL), which will support the accreditation in Romania of a specialized center in the analyses of the 17p chromosomal deletion, p53 mutation and IGHV status in CLL, in order to achieve European standards.

The result will be introduced in a data base a newly diagnosed patients, in which major prognostic markers will be emphasized. Besides a better prognostic evaluation, the available data will permit a better treatment option choice for each individual case – including new small-molecule agents (ex Bruton tyrosine kinase inhibitor, BCL-2 inhibitor, PI3K inhibitor). In a second stage, the diagnostic

evaluations made, will allow us to monitor the post-treatment response and evolution with an added capacity to detect relapsed cases earlier through MRD (minimal residual disease) evaluation, with a positive impact to treatment efficacy and monitoring.

Also, based on the techniques described above, we will be able to include the patients in further clinical studies and prospective observational studies.

2. The Development of a National CLL Patient Registry

The project's main objective is the establishment of a national CLL patient registry which will allow the systematic evolution follow-up of CLL patients. This objective supposes the development of an IT solution which will allow the efficient acquisition and processing of clinical and laboratory data – by using an acquisition "cross-platform" modular system of GIS data with mobile smart-devices extension; the creation of a statistical model for the identification of novel risk and prognostic factors in the evolution of these patients.

This patient registry will include data from the 1. Personalized medicine in hematology-oncology: Application of molecular genetics and cytometry techniques for the prognostic evaluation of patients with CLL project. By pairing these data sets we hope to obtain a statistically relevant characterization of Romanian CLL patients with the long term-objective of improving the management of these patients with this frequent malignant disorder.