

Proceedings from the 1st Insights in Hematology Symposium, Cluj-Napoca, Romania March 11-12, 2016

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In the March 2016 issue of the *Lancet Haematology*, the editorial office published a paper stating the roadmap for European research in hematology, based on the European Hematology Association (EHA) consensus document that outlines the directions in hematology for the following years across the continent. The meeting entitled “Insights in hematology” is organized a support for the initiative of a roadmap for European hematologists regarding research, may it be basic research or clinical research, but this consensus should not be focused mainly on European institutions, but rather form the backbone of global research between Europe and the United States, Japan or any other country. This will allow Europeans to learn as well as to share their experience with the rest of the scientific and medical community. And the Cluj-Napoca meeting should be followed by other such meetings all across the EU.

In the March 2016 issue of the *Lancet Haematology*, the editorial office published a paper stating the roadmap for European research in hematology, based on the European Hematology Association (EHA) consensus document that outlines the directions in hematology for the following years across the continent [1]. This consensus was established by a panel of approximately 300 experts across Europe and helps policy makers, funding bodies and a direction of where future efforts should be focused in order to maximize the impact of research in the medical community. Still, in the past few years human society has not been confined to a certain geographical area, to certain countries or to a certain continent. Globalization is a real fact and medicine must therefore adapt in order to provide the patient the best possible healthcare. In an effort to adapt to the reality that surrounds us, a consensus meeting was organized in the heart of

Transylvania on March 11-12, 2016. This consensus in Cluj-Napoca, entitled “Insights in hematology”, gathered experts from the two main cancer centers in Romania (“Ion Chiricuță” Oncology Institute and Fundeni Clinical Institute) along with experts from the United States, Norway, South Africa and Japan in order to discuss future collaboration projects in both basic and clinical research. Joint basic research projects will be developed between Romania and The Johns Hopkins University in Baltimore, The University of Texas MD Anderson Cancer Center in Houston and the University of Bergen, that will continue previously published data [2-4]. Taking into consideration that today a patient may travel from one part of the planet to the other in a matter of hours, serious public health problems such as endemic HIV infection may concern European physicians. Thus, a collaboration with South African hematologists is compulsory

[5, 6]. The last but not least direction in which we aim to focus our clinical research is stem cell transplantation, with a special emphasis on haplo-identical stem cell transplantation as Eastern European stem cell donor registries are not as well established as the ones in Western Europe and the US. Thus, a haploidentical stem cell transplantation may sometimes be the only curative option for a hematological malignancy [7]. This collaboration between Romanian hematologists and the MD Anderson Cancer Center has already facilitated the first haplo case in Romania, on a Hodgkin's lymphoma patient [8, 9].

Thus, we fully support the initiative of a roadmap for European hematologists regarding research, may it be basic research or clinical research, but this consensus should not be focused mainly on European institutions, but rather form the backbone of global research between Europe and the United States, Japan or any other country. This will allow Europeans to learn as well as share their experience with the rest of the scientific and medical community. And the Cluj-Napoca meeting be followed by other such meetings all across the EU.

Dr. Anca Bojan, Associate Professor of Hematology and attending physician in internal medicine and hematology at the "Ion Chiricuță" Oncology Institute, "Iuliu Hațieganu" University of Medicine and Pharmacy in Cluj-Napoca presented the importance of gold nanoparticles as carriers for various anti-leukemia drugs. So, she presented the results of a collaboration between Romania and Norway, in which we have successfully conjugated gold nanoparticles to either rituximab for the treatment of chronic lymphocytic leukemia, or with tyrosine kinase inhibitors (sorafenib, midostaurin, quizartinib and sorafenib) for the treatment of acute myeloid leukemia [10-12]. The data presented so far will be continued as a result of the collaboration with the University of Bergen, Norway.

Dr. Stefan Ciurea, Associate Professor of Cancer Medicine and Stem Cell Transplantation at the University of Texas MD Anderson Cancer Center in Houston, USA presented the haploidentical stem cell transplantation, with an emphasis on optimizing conditioning regimens by diagnosis, improving donor selection, and enhancing graft-*versus*-leukemia effect. Haploidentical related donors are an attractive alternative source of stem cells for allogeneic stem cell transplantation due to widespread availability and ease of stem cell procurement. Historically, haploidentical stem cell transplantation with extensive T-cell depletion has been associated with high rates of infectious complications and non-relapse mortality. Post-transplantation cyclo-

phosphamide has been shown to induce immune tolerance, effectively control graft-*versus*-host-disease and is associated with lower NRM, making it a preferred option for patients undergoing a haplo-identical stem cell transplantation [13].

Dr. Delia Dima, an attending physician in hematology at the "Ion Chiricuță" Oncology Institute presented the clinical management of chronic myeloid leukemia (CML), from therapy with tyrosine kinase inhibitors to stem cell transplantation. Dr. Dima presented a special emphasis on the prospective analysis of low-level BCR-ABL1 T315I mutation in CD34 + cells of patients with *de novo* chronic myeloid leukemia. The results of her research concluded that the T315I mutation, a negative prognostic factor for the terminal phase of chronic myelogenous leukemia treated with first- and second-line tyrosine kinase inhibitors, might be an indicator of allogeneic stem cell transplant as the treatment of choice [14].

Dr. Shigeo Fuji, attending physician in stem cell transplantation at the National Cancer Center in Tokyo, Japan presented the importance of stem cell transplantation for adult T cell leukemia/lymphoma, concluding that adult T-cell leukemia/lymphoma (ATL) relapse is a serious therapeutic challenge after allogeneic hematopoietic stem cell transplantation. This suggests that induction of a graft-*versus*-ATL effect may be crucial to obtaining durable remission for ATL patients with relapse or progression after allogeneic stem cell transplantation.

Dr. Gabriel Ghiaur, attending physician and Assistant Professor of Hematology at the Johns Hopkins University School of Medicine in Baltimore, USA presented the bone marrow niche and the molecular mechanisms of resistance to chemotherapy. The bone marrow microenvironment is responsible for difference between *in vitro* sensitivity and *in vivo* resistance of acute myeloid leukemia to all-trans retinoic acid-induced differentiation. Dr. Ghiaur suggests that stromal CYP26 activity creates retinoid low sanctuaries in the bone marrow that protect acute myeloid leukemia cells from systemic therapy. Inhibition of CYP26 provides new opportunities to expand the clinical activity of retinoic acid in both acute promyelocytic leukemia and other types of acute myeloid leukemia [15, 16].

Dr. Ravnit Grewal, senior consultant in hemato-pathology at the Stellenbosch University in Cape Town, South Africa presented the diagnosis and clinical management of HIV-associated lymphomas. The incidence of HIV-related lymphomas (HRLs) is increased by 60-100 times in patients with HIV. When compared to the general population, patients with HRLs often present with extranodal

lymphoid proliferation, most frequently of the gastrointestinal tract, central nervous system, liver and bone marrow. Since B-cell lymphomas arise from various stages of B-cell development in both HIV-infected and HIV-naïve patients, the joint research project between Cluj-Napoca and Cape Town attempts to determine the different miR signatures in B-cell development. As classic immunohistochemistry staining is sometimes not enough for the differential diagnosis of HRLs, in the present review, we have described the potential use of miRs in the prognosis and diagnosis of these diseases.

Dr. Emmet McCormack, Professor of Pharmacology and Clinical Sciences at the University of Bergen in Norway presented the animal models of acute leukemia he and his collaborators have developed in their department. One other important aspect in the development of xenograft models of acute myeloid leukemia is the possibility to use imaging techniques to monitor *in vivo* the progression of the disease. Imaging techniques also authorize the evaluation of the efficacy of an experimental treatment on tumor growth. This review will focus on the description of xenograft models of acute leukemia and will provide researchers and clinicians an overview of how these models have been used for the development of new therapeutic options and new imaging approaches to study acute leukemia *in vivo* [17, 18].

Dr. Alina Tănase, Associate Professor of Hematology and attending physician in stem cell transplantation at the Fundeni Clinical Institute, presented the management of aggressive lymphomas. Significant uncertainty exists in regard to the efficacy of maintenance therapy after high-dose chemotherapy as well as autologous stem cell transplantation for the treatment of patients with aggressive lymphoma. Post-transplant maintenance immune-targeting strategies, including PD-1/PD-L1 blocking antibodies, rituximab, and brentuximab, may improve progression-free survival but not overall survival. Collectively, the results indicate a need for testing new strategies with well-designed and adequately powered RCTs to better address the

role of post-transplant maintenance in relapsed/refractory lymphomas [19].

Dr. Adrian Trifa, attending physician in medical genetics and the “Ion Chiricuță” Oncology Institute presented the role CALR *versus* JAK in chronic myeloproliferative disease [20]. CALR-mutated essential thrombocythemia (ET) patients display a distinct phenotype compared to JAK2-mutated ET patients. This phenotype is characterized by higher platelet counts, lower WBC counts and a lower thrombotic risk. Interestingly, splenomegaly is less likely in CALR-mutated ET patients. Thus, CALR-mutated ET might represent a more benign entity than the JAK2-mutated one.

The symposium was closed by a presentation of **Dr. Ciprian Tomuleasa**, Research Assistant Professor at the “Iuliu Hațieganu” University of Medicine and Pharmacy in Cluj-Napoca, that presented his latest research conducted in collaboration with senior hematologists from the United States [21]. His research focused on developing a pharmacological screening for primary myelofibrosis, a study that once published is believed to change the landscape of how physicians look at primary myelofibrosis.

CONCLUSION

At present medicine progress can only be achieved through collaboration and sharing ideas. The current paper comes as the birth certificate for a research consortium in hematology between the two main medical centers from Romania: Bucharest and Cluj-Napoca. This consortium will form the future backbone of collaborations with institutions from all over the world, from Japan to Europe, Africa and the United States.

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În martie 2016, Lancet Haematology a publicat un editorial prin care este trasat ghidul cercetării în hematologia europeană, bazându-se pe consimțământul Asociației Europene de Hematologie. În Cluj-Napoca am inițiat organizarea simpozionului „Insights in hematology”, pentru a susține inițiativa trasării unei direcții de cercetare în hematologie, atât în laborator, cât și în clinică. Însă cercetarea nu ar trebui să fie doar între instituții europene, dar să includă și centre

medicale puternice din Japonia sau Statele Unite. Iar instituțiile europene să reprezinte coloana vertebrală a acestei colaborări. Astfel, vom permite europenilor să învețe cât mai mult din experiența altor medici și cercetători. Iar simpozionul ce va fi organizat anual în Cluj-Napoca să fie repetat și în alte centre universitare din Uniunea Europeană.

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