12ª ACTUALIZACIÓN en el TRATAMIENTO LEUCEMIA AGUDA 2023

del 5 al 7 OCT 2023

Dr. Elias Jabbour
MD Anderson Cancer Center, Houston, USA

My clinical mission is to improve the outcome of patients suffering from acute leukemia in general and acute lymphocytic leukemia in particular (ALL). As a hematologist and oncologist, I face challenges and unmet needs in this field almost every day. My academic career as a clinical investigator is thus devoted to tackle these challenges. The hallmark of ALL in the pediatric population is its treatment success with cure rates of ≥ 80%. This was achieved through the optimization of doses and schedules of the same chemotherapy agents used over the past forty years. However, similar strategies have not yielded comparable results in adult ALL, resulting in estimated cure rates of only 30%-40%. Major advances in the recent decade have been propelled by a greater understanding of the disease pathogenesis and improvement of prognostic groups, as well as the introduction of novel therapies that target specific subsets. Risk-adapted therapies are currently also producing significant improvements in survival. Therapies targeting either specific transcripts [e.g. BCR-ABL1 tyrosine kinase oncoprotein by tyrosine kinase inhibitors (TKIs)] or specific leukemic cell surface antigens (e.g. CD20, CD22, and CD19 monoclonal antibodies) are major breakthroughs in the treatment of ALL. As the section chief of ALL in MDACC s Leukemia Department, I have designed more than a dozen clinical trials assessing new combinations of treatments for the management of de novo ALL, Philadelphia (Ph)-positive ALL, elderly ALL, and relapsed/refractory disease. Of note, I developed a protocol that has shown significant improvements in survival rates for patients with Ph-positive ALL. Historically, these patients have poor outcomes, with a one-year survival rate of less than 10%. By combining H-CVAD chemotherapy with ponatinib, a new and potent TKI, the 3-year survival rate of these patients has increased to 76% and the 5-year rate to 71% (historically around 40%). This work was published in Lancet Oncology 2015 and recently updated in Lancet Hematology 2018. We showed that the outcomes of these patients can be improved through the suppression of the T315I clone, present in up to 25% of patients at baseline (detected by next generation sequencing [NGS]) and universally resistant to all TKIs except ponatinib, and by the induction of a complete molecular response. Our findings are challenging the current notion of the need of allogeneic stem cell transplantation (ASCT) in first remission. This new regimen may become a new standard of care for adult patients with this disease. I am leading a confirmatory multi-center Phase III trial in patients with newly diagnosed Ph-positive ALL.

Another area on which I focus my research is elderly patients with ALL. The aggressive biology of the disease and elderly patients poor tolerance of intensive chemotherapy leads to low survival rates for this patient population. I am currently investigating an innovative strategy combining new monoclonal antibodies such as inotuzumab ozogamicin, a conjugated anti-CD22 antibody, and blinatumomab, with minimal chemotherapy. This combination has proved to be safe and more effective than previous standards of care. So far, with more than 70 patients treated, the median survival is doubled compared with a historical series. These types of combination regimens will likely become the new standards of care in the near future. I will be leading 2 multicenter, randomized trial assessing inotuzumab and blinatuomab in frontline elderly ALL therapy. Furthermore, I am evaluating new combinations of targeted therapies plus chemotherapy with the aim to minimize toxicities and eradicate minimal residual disease, thereby increasing cure rates of adult patients with ALL to the high level achieved in pediatric patients.

B. Positions, Scientific Appointments, and Honors

Positions and Employment

2018-present

Professor, Department of Leukemia, Division of Cancer Medicine, MD Anderson Cancer Center, Houston, TX

2015-present

MD Anderson Cancer Center
Madrid • España

Section Chief, Acute Lymphocytic Leukemia, Department of Leukemia, Division of Cancer Medicine, The University of Texas MD Anderson Cancer Center, Houston, TX

2012-2018

Associate Professor, Department of Leukemia, Division of Cancer Medicine, The University of Texas MD Anderson Cancer Center, Houston, TX

2007-2012

Assistant Professor, Department of Leukemia, Division of Cancer Medicine, The University of Texas MD Anderson Cancer Center, Houston, TX

Other Experience and Professional Memberships

2011-present

Member, MDA Faculty Advisory Board, The University of Texas MD Anderson Cancer Center, Houston, TX

2008-present

Reviewer, Leukemia

Honors

2023

Ben Qurrah Award, National Arab American Medical Association

2022

King Hussein Lifetime Achievement Award for Cancer Research

2022

Presidential Lebanese Order of Merit Award

2021

D.B. Lane Cancer Research Fund Distinguished Professorship in Leukemia Research, D.B. Lane Cancer Research Fund

2020

2020 Faculty Achievement Award in Patient Care, MDACC

2019

2019 ALL Team Award

2018-2021

2018 Faculty Scholar Award, MDACC

2016

Celgene 2016 Young Investigator Award, Celgene Corporation

2007

Merit Award, American Society of Clinical Oncology

2007

Merit Award, American Society of Hematology

2007

The Celgene Future Leader in Hematology Award

2007

The Kimberly Patterson Fellowship in Leukemia Research Award

2007

The Shannon Timmins Fellowship for Leukemia Research Award

2006

Merit Award, American Society of Blood and Marrow Transplantation

2006

Merit Award, American Society of Clinical Oncology

2006

Merit Award, American Society of Hematology

2005

Merit Award, American Society of Clinical Oncology

2005

Merit Award, American Society of Hematology

C. Contributions to Science

1.

Acute lymphocytic leukemia. I am currently leading the acute lymphocytic leukemia (ALL) program in our department. I have designed more than a dozen protocols assessing new combinations for the management of de novo ALL, elderly ALL, and relapsed/refractory disease. Of note, Dr. I have recently led a research that shows a significant improvement in outcome for patients with Philadelphia-positive (Ph-positive) ALL. Historically, these patients had poor outcomes, with fewer than 10% surviving beyond one year. I developed a new regimen for these patients combining H-CVAD chemotherapy with ponatinib, a new and potent tyrosine kinase inhibitor. This combination has significantly improved survival of these patients, with 2-year survival rates of 80%. His work was recently published in Lancet Oncology. Another area of interest is elderly patients with ALL. The survival of these patients is poor due to the aggressive biology of the disease and the poor tolerance to intensive chemotherapy. I have been very innovative in combining new monoclonal antibodies such as inotuzumab with minimal chemotherapy. This combination has proved to be safe and more effective than chemotherapy used previously. Combination regimens such as this will likely become the standard of care in the near future. Furthermore, I have been evaluating new combinations of new targeted therapies with chemotherapy with the aim to minimize toxicities, eradicate minimal residual disease, and thus push the cure rates of adult patients with ALL to the high level achieved in pediatric leukemias. .

a.

Kantarjian H, Thomas D, Jorgensen J, Kebriaei P, Jabbour E, Rytting M, York S, Ravandi F, Garris R, Kwari M, Faderl S, Cortes J, Champlin R, O'Brien S. Results of inotuzumab ozogamicin, a CD22 monoclonal antibody, in refractory and relapsed acute lymphocytic leukemia. Cancer. 2013 Aug 1;119(15):2728-36. PubMed PMID: 23633004; PubMed Central PMCID: PMC3720844.

b.

Jabbour E, O'Brien S, Huang X, Thomas D, Rytting M, Sasaki K, Cortes J, Garcia-Manero G, Kadia T, Ravandi F, Pierce S, Kantarjian H. Prognostic factors for outcome in patients with refractory and relapsed acute lymphocytic leukemia treated with inotuzumab ozogamicin, a CD22 monoclonal antibody. Am J Hematol. 2015 Mar;90(3):193-6. PubMed PMID: 25407953.

2.

Chronic myeloid leukemia. Another important part of my research is to address the question of resistance to tyrosine kinase inhibitors and to analyze the outcome of these patients. I have identified different mechanisms of resistance such as mutations in the kinase domain of the oncoprotein and described the clinical significance of them. In a second step, I assessed the efficacy of various salvage therapies, including allogeneic bone marrow transplantion, farnesyl transferase inhibitors, hypomethylating agents, second generation tyrosine kinase inhibitors and other agents. In the case of second-generation tyrosine kinase inhibitors, he showed that there was no cross-resistance between the different agents and no cross-intolerance, with each drug having a different safety profile. I was also able to confirm the in vitro mutagenesis model, where each agent can induce specific mutations in vivo. In other words, I reported the sensitivity of specific mutations to individual drugs and that the drugs can induce certain mutations. The clinical significance of this is that we can use the model to tailor CML therapy to individual patients by safety profile and mutation profile, and to identify those who might benefit from combination therapy. My work in chronic myeloid leukemia establishing new milestones leading to personalized therapy has been a great asset for the management of this rare disease. My work has been published in peer reviewed journals and was adapted by major groups such as the National Comprehensive Cancer Network (NCCN) and the European Leukemia Net (ELN). These associations have tremendous impact at the scientific and financial levels.

a.

Jabbour E, Kantarjian H, O'Brien S, Shan J, Quintas-Cardama A, Faderl S, Garcia-Manero G, Ravandi F, Rios MB, Cortes J. The achievement of an early complete cytogenetic response is a major determinant for outcome in patients with early chronic phase chronic myeloid leukemia treated with tyrosine kinase inhibitors. Blood. 2011 Oct 27;118(17):4541-6; quiz 4759. PubMed PMID: 21803854; PubMed Central PMCID: PMC3291489.

b.

Jabbour E, Kantarjian HM, O'Brien S, Shan J, Quintás-Cardama A, Garcia-Manero G, Rios MB, Cortes JE. Front-line therapy with second-generation tyrosine kinase inhibitors in patients with early chronic phase chronic myeloid leukemia: what is the optimal response? J Clin Oncol. 2011 Nov 10;29(32):4260-5. PubMed PMID: 21990394; PubMed Central PMCID: PMC3221527.

c.

Jabbour E, Cortes J, Nazha A, O'Brien S, Quintas-Cardama A, Pierce S, Garcia-Manero G, Kantarjian H. EUTOS score is not predictive for survival and outcome in patients with early chronic phase chronic myeloid leukemia treated with tyrosine kinase inhibitors: a single institution experience. Blood. 2012 May 10;119(19):4524-6. PubMed PMID: 22431574; PubMed Central PMCID: PMC3362365.

d.

Jabbour E, Kantarjian HM, Saglio G, Steegmann JL, Shah NP, Boqué C, Chuah C, Pavlovsky C, Mayer J, Cortes J, Baccarani M, Kim DW, Bradley-Garelik MB, Mohamed H, Wildgust M, Hochhaus A. Early response with dasatinib or imatinib in chronic myeloid leukemia: 3-year follow-up from a randomized phase 3 trial (DASISION). Blood. 2014 Jan 23;123(4):494-500. PubMed PMID: 24311723; PubMed Central PMCID: PMC4190618.

3.

Myelodysplastic syndromes (MDS). Additionally, I am interested in the assessment of genomic instabilities in patients with low-risk myelodysplastic syndromes (MDS) who may need earlier therapeutic intervention. Currently, these so-called low-risk patients are monitored and only offered supportive care. Identifying patients at risk and applying earlier intervention may significantly improve their prognosis. I am leading the first multicenter US study randomizing patients with low-risk MDS to early intervention with hypomethylathing agents versus watch and wait strategy. This study will have an enormous impact of the management of these patients. Furthermore, I recently analyzed the outcome of patients with MDS who fail therapy with hypomethylating agents and found that the median survival was four months, highlighting the urgent need for new salvage therapies. Interestingly enough, I discovered that our new classification system is applicable at the time of treatment failure as well. Thus, we can divide relapsed/refractory patients into two categories: those with more aggressive disease and worse prognosis, and those with a more indolent course. I will use this discovery as a baseline tool to design clinical trials for treatment of such patients. Options range from allogeneic bone marrow transplantation with a modern, less toxic conditioning regimen; to combination therapies with hypomethylating agents and histone deacetylase inhibitors; to agents with novel mechanisms of actions.

a.

Takahashi K, Jabbour E, Wang X, Luthra R, Bueso-Ramos C, Patel K, Pierce S, Yang H, Wei Y, Daver N, Faderl S, Ravandi F, Estrov Z, Cortes J, Kantarjian H, Garcia-Manero G. Dynamic acquisition of FLT3 or RAS alterations drive a subset of patients with lower risk MDS to secondary AML. Leukemia. 2013 Oct;27(10):2081-3. PubMed PMID: 23774633.

b.

Jabbour E, Takahashi K, Wang X, Cornelison AM, Abruzzo L, Kadia T, Borthakur G, Estrov Z, O'Brien S, Mallo M, Wierda W, Pierce S, Wei Y, Sole F, Chen R, Kantarjian H, Garcia-Manero G. Acquisition of cytogenetic abnormalities in patients with IPSS defined lower-risk myelodysplastic syndrome is associated with poor prognosis and transformation to acute myelogenous leukemia. Am J Hematol. 2013 Oct;88(10):831-7. PubMed PMID: 23760779; PubMed Central PMCID: PMC3923606.

c.

Jabbour E, Ghanem H, Huang X, Ravandi F, Garcia-Manero G, O'Brien S, Faderl S, Pierce S, Choi S, Verstovsek S, Brandt M, Cortes J, Kantarjian H. Acute myeloid leukemia after myelodysplastic syndrome and failure of therapy with hypomethylating agents: an emerging entity with a poor prognosis. Clin Lymphoma Myeloma Leuk. 2014 Apr;14(2):93-7. PubMed PMID: 24447728; PubMed Central PMCID: PMC4098769.

d.

Jabbour EJ, Garcia-Manero G, Strati P, Mishra A, Al Ali NH, Padron E, Lancet J, Kadia T, Daver N, O'Brien S, Steensma DP, Sekeres MA, Gore SD, Dezern A, Roboz GJ, List AF, Kantarjian HM, Komrokji RS. Outcome of patients with low-risk and intermediate-1-risk myelodysplastic syndrome after hypomethylating agent failure: a report on behalf of the MDS Clinical Research Consortium. Cancer. 2015 Mar 15;121(6):876-82. PubMed PMID: 25410759; PubMed Central PMCID: PMC4378905.

4.

Acute myeloid leukemia. I have led the design of new clinical trials for patients with AML. I have led the efforts to test triple therapy in AML (nucleoside analogs + anthracyclines + cytarabine). The interim results from this randomized trial show a significant improvement in outcome in patients who receive the nucleoside analog clofarabine. This may change the standard of care for the management of patients with AML.

a.

Jabbour E, Garcia-Manero G, Cortes J, Ravandi F, Plunkett W, Gandhi V, Faderl S, O'Brien S, Borthakur G, Kadia T, Burger J, Konopleva M, Brandt M, Huang X, Kantarjian H. Twice-daily fludarabine and cytarabine combination with or without gentuzumab ozogamicin is effective in patients with relapsed/refractory acute myeloid leukemia, high-risk myelodysplastic syndrome, and blast- phase chronic myeloid leukemia. Clin Lymphoma Myeloma Leuk. 2012 Aug;12(4):244-51. PubMed PMID: 22534616; PubMed Central PMCID: PMC3859239.

strategy. This study will have an enormous impact of the management of these patients. Furthermore, I recently analyzed the outcome of patients with MDS who fail therapy with hypomethylating agents and found that the median survival was four months, highlighting the urgent need for new salvage therapies. Interestingly enough, I discovered that our new classification system is applicable at the time of treatment failure as well. Thus, we can divide relapsed/refractory patients into two categories: those with more aggressive disease and worse prognosis, and those with a more indolent course. I will use this discovery as a baseline tool to design clinical trials for treatment of such patients. Options range from allogeneic bone marrow transplantation with a modern, less toxic conditioning regimen; to combination therapies with hypomethylating agents and histone deacetylase inhibitors; to agents with novel mechanisms of actions.

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b.

Nazha A, Kantarjian H, Ravandi F, Huang X, Choi S, Garcia-Manero G, Jabbour E, Borthakur G, Kadia T, Konopleva M, Cortes J, Ferrajoli A, Kornblau S, Daver N, Pemmaraju N, Andreeff M, Estrov Z, Du M, Brandt M, Faderl S. Clofarabine, idarubicin, and cytarabine (CIA) as frontline therapy for patients ≤60 years with newly diagnosed acute myeloid leukemia. Am J Hematol. 2013 Nov;88(11):961-6. PubMed PMID: 23877926; PubMed Central PMCID: PMC4110914.

c.

Jabbour E, Daver N, Champlin R, Mathisen M, Oran B, Ciurea S, Khouri I, Cornelison AM, Ghanem H, Cardenas-Turanzas M, Popat U, Ravandi F, Giralt S, Garcia-Manero G, Cortes J, Kantarjian H, de Lima M. Allogeneic stem cell transplantation as initial salvage for patients with acute myeloid leukemia refractory to high-dose cytarabine-based induction chemotherapy. Am J Hematol. 2014 Apr;89(4):395-8. PubMed PMID: 24375514; PubMed Central PMCID: PMC4140180.