BMT News

Winter 2016

An update from The Blood and Marrow Transplant Program at Northside Hospital

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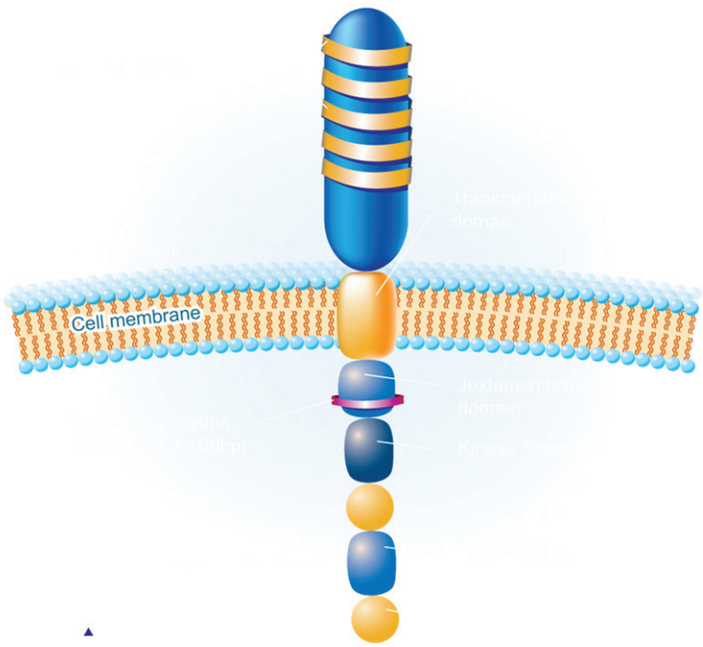

Inhibition of FLT3 Following Allogeneic Transplants

Acute myeloid leukemia (AML) is the most common form of acute leukemia in adults, with just over 20,000 projected new cases in the U.S. in 2015. The prognosis for patients with AML varies by subtype but more than 50% of patients eventually fail therapy.[1] The presence of cytogenetic abnormalities or of leukemia-associated gene mutations are important prognostic indicators for risk of relapse and responsiveness to chemotherapy.[2] The most common mutation in AML with normal cytogenetics is an internal tandem duplication of the juxtramembrane domain of the FMS-like tyrosine kinase 3 (FLT3) gene (FLT3-ITD) and has been found in to be a strong negative predictor of patient outcome.[3,4]

FLT3 plays a role in normal growth and differentiation of hematopoietic precursor cells. Binding of ligand to the FLT3 receptor results in autophosphorylation and activation of a host of

downstream effector signaling cascades. These include RAS/MEK, P13K/AKT/mTOR, and STAT-5 pathways, all of which play roles in in the promotion of cell cycle progression, inhibition of apoptosis, and activation of differentiation. FLT3 expression is normally lost as hematopoietic progenitor cells differentiate and mature. However, in AML, overexpression of the FLT3 receptor may occur in leukemia cells leading to malignant blast proliferation. AML patients with FLT3-ITD experience ligand-independent FLT3 dimerization and signal activation resulting in increased proliferation and reduced susceptibility to apoptosis in hematopoietic cells.[3,5] AML patients with FLT3-ITD mutations therefore present with higher white blood cell counts and percentage of blasts in the peripheral blood and bone marrow than AML patients without this mutation.[6,7]

To date, there is no defined optimal treatment approach for patients with FLT-ITD AML. With standard induction chemotherapy these patients can expect a complete response (CR) rate roughly equivalent to that of patients with wild type FLT3 (FTLs-WT). However, patients with the FLT3-ITD mutation patients experience a much higher relapse rate and poor response to salvage therapy than patients without this mutation. Many retrospective studies have suggested that allogeneic hematopoietic transplantation (HSCT) following the achievement of CR1 results in lower relapse rates than conventional consolidation chemotherapy. It has therefore become the preferred post-remission therapy for such patients[8-10] Nevertheless, relapse of AML after transplant remains the main obstacle to long-term survival in patients with FLT3-ITD. New maintenance treatments which could improve relapse rates after allogeneic HSCT may be of significant benefit to this population.

Inhibition of FLT3 kinase activity post-transplant has the potential to decrease relapse among patients with FLT3-ITD AML who undergo allogeneic HSCT. Several small molecule inhibitors of the FLT3 tyrosine kinase have been developed in recent years. These including sorafenib, lestaurtinib (CEP-701), midostaurin (PKC412), and quizartinib (AC220). However, they have not been extensively studied within this context. Sorafenib is a multikinase inhibitor currently FDA approved for the treatment of advanced renal cell cancer and some other solid tumors. In a recently published phase I trial the maximum tolerated dose of sorafenib when used as maintenance therapy for FLT3-ITD positive AML starting day 45-120 post allogeneic HSCT was 400 mg twice daily. One year progression-free survival was 85%.[11] Midostaurin is an oral multitarget protein kinase inhibitor shown to inhibit both mutated and wild-type FLT3 kinase as well as multiple other molecular targets thought to be important for the pathogenesis

of AML. These targets include VEGFR-1, c-kit, H- and K-ras as well as the multidrug resistant gene MDR. Midostaurin was recently studied in both the upfront treatment and in the relapsed/refractory AML setting. In addition to indicators of activity, these phase I and II studies showed midostaurin to be well tolerated with common side effects being nausea, vomiting, diarrhea, and myelosuppression. As relapse remains an important cause of treatment failure following allogeneic HSCT for FLT3-ITD positive AML, an important consideration is whether FLT3 inhibition post-transplant can delay or prevent relapse post HSCT in such patients.

NSH 1114 is a phase II, randomized comparative trial of standard of care, with or without midostaurin to prevent relapse following allogeneic HSCT in patients with FLT3-ITD mutated acute myeloid leukemia. This will provide a novel option for patients with FLT3-ITD AML to prevent relapse following HSCT who would otherwise be expected to have a poor prognosis. The intent of this study is to evaluate whether the addition of midostaurin to standard of care following allogeneic HSCT improves Relapse Free Survival (RFS) in FLT3-ITD AML patients in CR1. Additionally, this study will provide prospective outcome data for FLT3-ITD AML after transplantation, which is currently lacking. Laboratory correlates will evaluate endpoints such as FLT3 inhibition and FLT3 ligand levels in the plasma, the pharmacokinetic association between midostaurin exposure and FLT3 inhibition and clinical outcome, and the mutation status prior to enrollment into the study compared to status at relapse. Eligible patients must be between 18 and 60 years of age, have documented FLT3 ITD mutation, and have undergone an allogeneic HSCT in CR1 from a matched related or unrelated donor. Patients will receive oral midostaurin or standard of care continuously for up to one year or disease relapse or withdrawal from study.

For further information regarding this trial, please contact Stacey Brown at Stacey.brown@northside.com or (404) 851-8238.

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We are Pleased to Announce Dr. Melhem Solh Joined BMTGA and NSH-BMT/Leukemia Programs

Prior to joining our team, Dr. Solh was the clinical director for the Florida Center for Cellular Therapy Bone Marrow Transplant Program, medical director for the Cellular Therapy Laboratory and an assistant professor of Medicine at the University of Central Florida. Dr. Solh is a board-certified hematologist and oncologist. At the University of Minnesota, Dr. Solh completed a hematology, oncology and blood and marrow transplant fellowship training program.

Dr. Solh has authored and co-authored over 40 abstracts and publications in peer reviewed journals: Biology of Blood and Marrow Transplant, Bone Marrow Transplantation, American Journal of Hematology. Dr. Solh's clinical research interests include the development of innovative therapies for leukemia and malignant blood disorders.

Dr. Solh is seeing new patients and can be reached at 404-255-1930.

NSH-BMT/Leukemia Program Presents at Atlanta MDS Foundation's Patient and Family Forum

On August 15, 2015, Northside Hospital-Blood and Marrow Transplant/Leukemia physician, Dr. Melhem Solh and NSH-Leukemia Program coordinators, spoke at the Atlanta MDS Foundation's Patient and Family Forum held at the Hyatt Atlanta Perimeter at Villa Christina. Over fifty patients and family members joined the MDS Foundation and NSH-BMT/Leukemia program in this patient educational meeting. The NSH-BMT/Leukemia program is a designated Center of Excellence (COE) for the MDS Foundation.

Topics discussed included: new clinical research trials, disease education and support organizations. NSH-Leukemia Program coordinators reviewed and discussed the MDS Foundation's "Building Blocks of Hope" that can be found on the MDS Foundation's website, www.mds-foundation.org, and the BMTGA website, bmtga.com.

For additional MDS Foundation resources and support, please call 1-800-MDS-0839, e-mail patientliaison@mds-foundation.org, or write, The MDSFoundation 4573 South Broad St., Suite 150, Yardville, NJ 08620.

mds foundation
the myelodysplastic syndromes foundation, inc.

Northside Hospital's #FaceLeukemia Campaign Gives Patients Social Media Platform to Raise Community Awareness of Complex Blood Cancer

For the September 2015 Blood Cancer Awareness Month, Northside Hospital in conjunction with the NSH-Leukemia Program, launched a month-long feature following the recent journeys of four leukemia patients through their diagnosis, treatment and recovery.

Our hope is that their stories will bring awareness to the struggles they faced battling cancer and to inspire you as much as they have inspired us to support leukemia research at Northside and Northside's leukemia programs. Please go to northside.com/leukemia for additional NSH- Leukemia Program information.

Please view NSH-Leukemia patient journeys from illness to wellness on www.northside.com or on social media use #faceleukemia and join us on https://www.facebook.com/NorthsideHosp; https://twitter.com/NorthsideHosp and https://instagram.com/northsidehosp/.

Tee off for BMT

The 23rd annual Northside Hospital Charity Golf Classic held on May 18, 2015 was a success. The tournament raised $480,000 and the proceeds go to the Cancer Research and Blood and Marrow Transplant funds. For more information on this year's event, check out this newsletter's back page.

NSH-BMT Clinical Pharmacy Helps Develop New Foundation for Cellular Therapies (FACT) 6th Edition Cellular Therapy Pharmacy Standard Requirements

NSH-BMT and Leukemia Clinical PharmD team

Connie Sizemore, NSH-BMT program's lead PharmD, was asked to participate on a new FACT Pharmacy sub-committee to develop pharmacy standards for blood and marrow transplant programs throughout the United States. Ms. Sizemore, as well as the entire team of NSH-BMT clinical pharmacists, have been recognized nationally for their expertise in providing patients with state-of-the-art blood and marrow transplant pharmacy services.

On October 28th, Ms. Sizemore participated in a national FACT Pharmacy sub-committee webinar where the new 6th Edition Cellular Therapy pharmacy standards were reviewed and examples for how to comply with the new standards was discussed.

BMT Protocols

NSH 927	Defibrotide for Patients With Hepatic VOD: A Treatment IND Study
NSH 988	BMT CTN 1101 - Multi-Center, Phase III, Randomized Trial of Reduced Intensity Conditioning (RIC) and Transplantation of Double Unrelated Umbilical Cord Blood versus HLA-Haploidentical Related Donor Bone Marrow for Patients with Hematologic Malignancies
NSH 1048	Easy-to-Read Informed Consent (ETRIC) for Hematopoietic Cell Transplantation Clinical Trials
NSH 1074	A Phase II Trial of Nonmyeloablative Haploidentical Peripheral Blood Stem Cell Transplantation followed by Maintenance Therapy with the Novel Oral Proteasome Inhibitor, MLN9708, in patient with High-risk Hematologic Malignancies.
NSH 1096	A Multi-center Phase II Trial of Randomized Novel Approaches for Graft-versus-Host Disease Prevention Compared to Contemporary Controls
NSH 1107	A Phase II Trial of High-dose Bendamustine, Etoposide, Cytarabine, and Melphalan (BeEAM) in the Up-front Treatment of Multiple Myeloma
NSH 1108	BMT-CTN- 1301-A Randominzed, Mulit-Center Phase III Trial of Calcineurin Inhibitor-Free Interventions for Prewvention of Graft Versus Host-Disease
NSH 1114	A Phase II, randomized, comparative trial of standard of care, with or without midostaurin to prevent relapse following allogeneic hematopoietic stem cell transplantation in patients with FLT3-ITD mutated acute myeloid leukemia
NSH 1125	BMT CTN -1302 - A Multicenter Phase II, Double-blind Placebo Controlled Trial of Maintaencance Ixazomib after Allogeneic Hematopoietic Stem Cell Transplantation for High Risk Multiple Myeloma Leukemia/Lymphoma/Multiple Myeloma

Leukemia/Multiple Myeloma/Lymphoma Protocols

C-175	A Phase 2 Randomized Open-label Study of MEDI-551 in Adults With Relapsed or Refractory DLBCL
C-225	A Phase 2b, Open-Label, Single-Arm Study of Selinexor (KPT-330) plus Low-Dose Dexamethasone in Patients with Multiple Myeloma Quad-refractory to Previous Therapies
NSH 1099	E1910 - Phase 3 randomized trial of blinatumomab for newly diagnosed BCR-ABL negative B-ALL in adults

NSH 1115	A Multi-Center Phase I/Ib Study Evaluating the Efficacy and Safety of the Novel PI3k Delta Inhibitor TGR-1202 in Combination with Ibrutinib in Patients with Select B-Cell Malignancies
C-203	Gemtuzumab Ozogamicin (Mylotarg®) Expanded Access Protocol for Treatment of Patients in the United States with Relapsed/Refractory Acute Myelogenous Leukemia Who May Benefit From Treatment and Have No Access to Other Comparable/Alternative Therapy
C-209	An Open-Label Phase 2 Prospective Randomized, Controlled Study of CLE-008 Myeloid Progenitor Cells as a Supportive Measure During Induction Chemotherapy for AML

Supportive Care Protocols

NSH 721	NMDP Recipient Consent for Participation in Registry, Research Database, and Research Sample Repository
NSH 888	The Impact of Hematopoietic Stem Cell Transplantation on Primary Caregiver Level of Burden and Distress
NSH 943	A multicenter access and distribution protocol for unlicensed cryopreserved cord blood units (CBUs) for transplantation in pediatric and adult patients with hematologic malignancies and other indications
NSH 995	A Multicenter safety study of unlicensed, investigational cryopreserved cord blood units (CBUs) manufactured by the National Cord Blood Program (NCBP) and provided for unrelated hematopoietic stem cell transplantation of pediatric and adult patients
NSH 1017	Prospective Multi-Center Cohort for the Evaluation of Biomarkers Predicting Risk of Complications and Mortality Following Allogeneic Hematopoietic Cell Transplant (HCT)
NSH 1095	Collection of Bone Marrow and Peripheral Blood (PB) samples from patients with leukemia and PB from the BM donors (BMD) to identify Leukemia-Specific Antigens (LSA) and Graft Versus Host Disease Antigens (GVHDA) for use in cellular immunotherapy
NSH 1113	A Phase 2b, Randomized, Double-Blind, Placebo-Controlled Multi-Center Study Evaluating Antiviral Effects, Pharmacokinetics, Safety, and Tolerability of GS-5806 in HCT Recipients with Respiratory Syncytial Virus (RSV) Infection of the Upper Respiratory Tract

Events Calendar

BLOOD AND MARROW TRANSPLANT CLINICAL TRIALS NETWORK

GA ncorp NCI Community Oncology Research Program

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