To conclude, Dr Fink noted that another study [Macbeth et al. ASH 2014 (abstr 3606)] showed similar results regarding lenalidomide inducing ubiquitination of CSNK1A1 by the CRBN-CRL4 and its subsequent degradation.

Th17-Prone CD146$^+$CCR5$^+$ T-Cell Population Is an Early Marker of Intestinal GVHD

Written by Maria Vinall

Acute graft-vs-host disease (GVHD) is a major complication of allogeneic hematopoietic stem cell transplantation (HSCT), primarily affecting the skin, liver, and gastrointestinal (GI) tract. GVHD limits the role of transplantation in other clinical settings, such as the treatment of severe autoimmune disorders. T lymphocytes in the peripheral blood play a central role in immunity and in the process whereby newly transplanted donor cells attack the transplant recipient's body.

In a late-breaking clinical trial [Li W et al. *Blood*. 2014], Wei Li, MD, PhD, Indiana University, Indianapolis, Indiana, USA, reported that early quantification of a novel Th17-prone CD146$^+$CCR5$^+$ inducible T-cell costimulator (ICOS)–induced population may identify patients at risk for GI GVHD development and subsequent mortality.

Peripheral blood cells from 214 HSCT patients (71 GI GVHD, 48 no GVHD, 33 non-GVHD enteritis, 22 skin-first GVHD, 40 isolated-skin GVHD) were analyzed using proteomics 14 days prior to the onset of GVHD symptoms. Biomarkers that increased 1.5-fold were identified in the plasma from GI GVHD patients and compared with HSCT patients without GVHD at matched time points. Two proteins were identified: CD146, a cell adhesion and trafficking molecule expressed on a subset of CD4$^+$ T cells and endothelial cells, and the chemokine (C-C motif) ligand 14, which binds to the chemokine receptor CCR5 on T cells.

CD146$^+$CCR5$^+$ T-cell frequency was significantly increased in patients with GI GVD compared with patients without GVHD ($P < .0001$), non-GVHD enteritis ($P < .0001$), or isolated-skin GVHD ($P = .007$) but not with skin-first and then GI GVHD ($P = .28$).

CD146$^+$CCR5$^+$ T cells were not correlated with GI histologic severity and increased prior to GVHD clinical onset. CD146$^+$CCR5$^+$ T cells were Th17 prone in that Th17 cells express more CD146 than Th1 cells. The activation marker ICOS, known to be critical for the development of human Th17 cells, was also critical for the expression of CD146$^+$CCR5$^+$ on T cells.

Th17 cells migrated more efficiently through endothelial-cell monolayers than their Th1 counterparts, suggesting that endothelium may play an important role in recruiting pathogenic T cells. This was supported by evidence showing that CD146 Th17 transmigration is reduced by CD146 shRNA knockdown on T cells. However, knockdown of CD146 on endothelial cells does not reduce T-cell transmigration.

Finally, to evaluate the in vivo function of CD146 T cells, donor human T cells knockdown with CD146shRNA were transmigrated into a xenogeneic GVHD mouse model. Mice did not lose weight, had similar human T-cell engraftment (hCD4), had fewer splenic CD146$^+$CCR5$^+$T cells, and expressed less interferon gamma 53 days after transplant, providing proof that CD146 promotes infiltration of pathogenic T cells into GVHD target organs.

The CD146$^+$CCR5$^+$ cell population is a biomarker of GI GVHD. Early quantification of this population of cells may predict the development of GI GVHD and offer more specific prevention and therapeutic strategies, thereby reducing mortality.

Sorafenib as Effective Treatment for Newly Diagnosed AML in Younger Patients

Written by Maria Vinall

Christoph Röllig, MD, Universitätsklinikum Dresden, Dresden, Germany, presented the results of the Study Evaluating Sorafenib Added to Standard Primary Therapy in Patients With Newly Diagnosed Acute Myeloid Leukemia Less Than 60 Years of Age [SORAML; Röllig C et al. ASH 2014 (abstr 6)]. Although overall survival (OS) was not different compared with placebo, sorafenib significantly improved event-free survival (EFS) and relapse-free survival (RFS) with a cost of higher incidence of infections and bleeding events in younger patients with acute myeloid leukemia (AML).

AML is the most common form of leukemia in adults [National Cancer Institute. http://www.cancer.gov/cancertopics/pdq/treatment/adultAML/Patient/page1. Accessed December 23, 2014]. Survival rate for this disease continues to remain unsatisfactory, particularly among patients aged > 60 years. The significant genetic diversity and abnormality in AML even within a tumor of a single individual make it difficult to treat [Cancer Genome Atlas Research Network. *N Engl J Med*. 2013]. Kinase mutations

are among the most frequently found genetic abnormalities. Mutations in the tyrosine kinase genes KIT and FLT3, and aberrant VEGF signaling through tyrosine kinases, play a critical role in AML biology. Sorafenib is a multikinase inhibitor with activity against several serine/threonine kinases and receptor tyrosine kinases.

SORAML was a randomized, multicenter, double-blind trial comparing sorafenib with placebo as an add-on to standard induction and consolidation treatment in 276 newly diagnosed AML patients aged 18 to 60 years with Eastern Cooperative Oncology Group (ECOG) performance 0 to 2, and adequate renal and liver function [Röllig C et al. ASH 2014 (abstr 6)]. Induction therapy consisted of 2 cycles of daunorubicin (60 mg/m^2 days 3 to 5, plus cytarabine 100 mg/m^2 cont. inf. days 1 to 7), followed by 3 cycles of high-dose cytarabine consolidation (3 g/m^2 BID days 1, 3, and 5). Allogeneic stem cell transplantation was scheduled in the first complete remission. Patients were randomized (1:1) to receive sorafenib (800 mg/day) or placebo as an add-on to standard treatment. The primary end point was EFS. Secondary end points included RFS, OS, complete remission rate, and incidence of adverse events (AEs).

Demographic and disease characteristics were equally distributed between the two arms. The incidence of FLT3-internal tandem duplication (ITD) and NPM1 mutation was 17% and 33%, respectively. Median drug dose was approximately 16 200 mg with significantly less intake in the sorafenib arm, most likely due to side effects. Complete remission was evident in 60% of sorafenib-treated patients compared with 59% of placebo-treated patients (P = .764). EFS was 9.2 months and 20.5 months in the placebo and sorafenib groups, respectively, corresponding to a 3-year EFS of 22% vs 40% (P = .013; Figure 1).

RFS was also significantly (P = .017) improved with sorafenib (56% after 3 years) treatment compared with placebo (38%), with a median RFS of 23 months with placebo compared with not yet reached after sorafenib treatment. At this point, there is no clear benefit for sorafenib treatment regarding OS (P = .382; Figure 2).

In the 46 FLT3-ITD-positive patients, there was no difference in EFS, but there was a trend for prolonged RFS and OS in favor of sorafenib. The relative risk for the occurrence of grade ≥ 3 AEs was significantly higher for hand-foot syndrome, diarrhea, bleeding, rash, liver toxicity, and fever in the sorafenib arm compared with the placebo arm.

In this first randomized trial, sorafenib plus chemotherapy comprise a feasible treatment strategy in younger AML patients and are associated with improved outcomes.

Figure 1. Sorafenib Significantly Improves Event-Free Survival

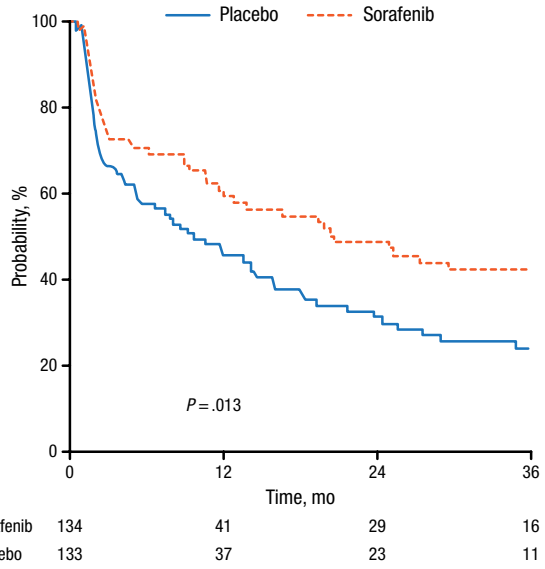

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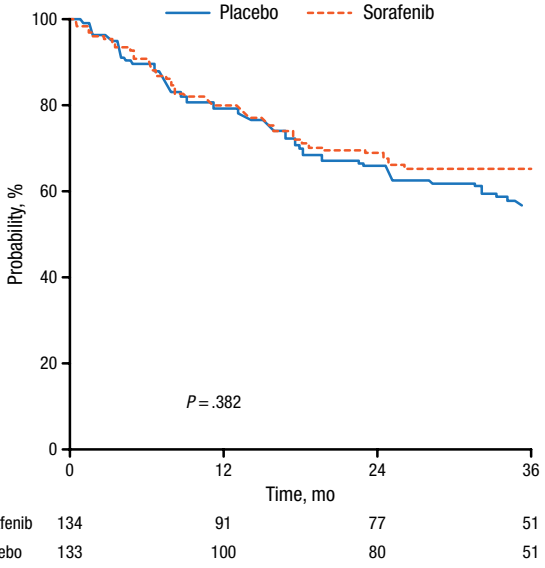
Figure 2. Sorafenib Does Not Improve Overall Survival Compared With Placebo



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