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October 5, 2018 • Volume 40, Number 19

oncology-times.com

ONCOLOGY TIMES®

Independent News on HEMATOLOGY / ONCOLOGY

New Treatments for Relapsed Hematologic Malignancies After alloHCT

BY JACQUELINE S. GARCIA, MD, & MATTHEW S. DAVIDS, MD, MMSc

Relapse remains the leading cause of treatment failure for patients with hematologic malignancies who undergo allogeneic hematopoietic cell transplantation (alloHCT). For example, patients with acute myeloid leukemia (AML) who relapse shortly after transplant have a particularly poor outcome, with a 3-year overall survival rate of <5 percent (*Biol Blood Marrow Transplant* 2015;454-459). Such patients commonly receive intensive chemotherapy, but outcomes with this approach are often poor. Therefore, therapeutic strategies to augment a graft-versus-tumor (GVT) effect without eliciting graft-versus-host disease (GVHD) have been explored.

CME Article

However, these strategies, such as withdrawal of immunosuppression, donor lymphocyte

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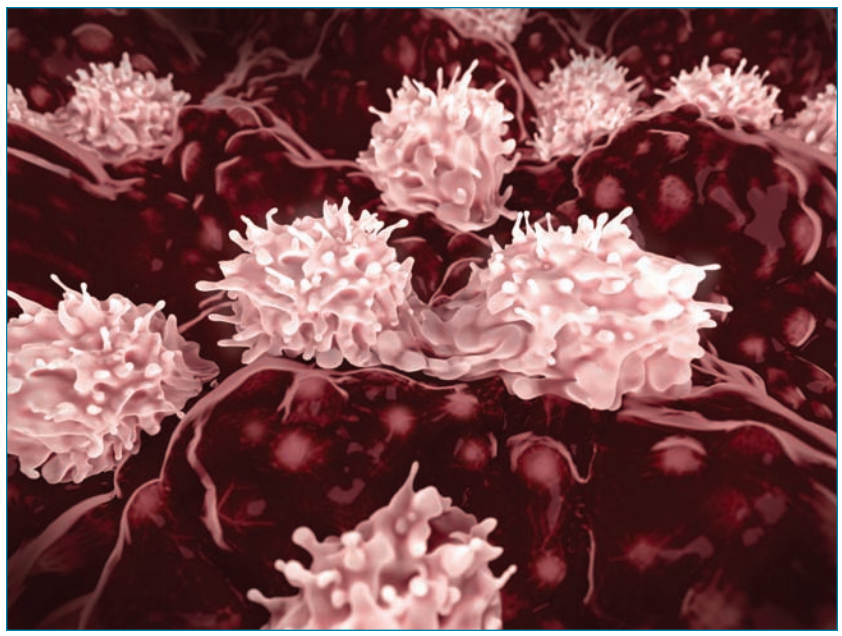

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Pioneer Takes Aim at Solid Tumors With T Cells

BY VALERIE NEFF NEWITT

Great men and women of medicine were once impressionable children. Their individual paths were gradually mapped by diverse experiences, directional inspirations, demanding education, and extreme intellectual curiosity.

For Steven A. Rosenberg, MD, PhD, Chief of the Surgery Branch at the NCI, one of history's darkest periods guided him toward a monumental career enveloping medical "firsts" that continue to shape the emerging potential of adoptive cell therapies (ACT) and the aggregate field of oncology.

"My parents were born in Poland and came here to escape persecution," said Rosenberg speaking by phone from his Bethesda, Md., office. "I was born in 1940. When I was 5 or 6 years old, virtually all of my parents' families were wiped out in the Holocaust. I remember seeing postcards arriving in the mail saying this relative died at Auschwitz, and that relative died at Buchenwald. It was a horrible experience. I learned that people could be evil; I wanted to be the opposite. Oh sure, I originally wanted to be a cowboy. But by 6 years of age, I converted to medicine."

That conversion eventually resulted in Rosenberg earning a PhD in biophysics, graduating from medical school, and embracing an early belief in the power

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Solving a Central Mystery of a Baffling High-Risk Leukemia

St. Jude Children's Research Hospital investigators have unraveled the origins and identified mutations associated with a perplexing form of acute leukemia. The landmark study lays the foundation for more effective treatment of patients with the high-risk cancer (*Nature* 2018; https://doi.org/10.1038/s41586-018-0436-0).

The research focused on mixed phenotype acute leukemia (MPAL), a subtype of acute leukemia that accounts for about 3 percent of the estimated 3,500 pediatric cases of acute leukemia diagnosed annually in the U.S. MPAL also occurs in adults. Their treatment is complicated because MPAL does not fit cleanly into a single diagnosis, but it includes features of both acute lymphoblastic leukemia (ALL) and acute myeloid leukemia (AML). These markers, which help determine treatment, sometimes change with time or treatment, in some cases enough to change the diagnosis from MPAL to AML or vice versa.

"ALL and AML have very different treatments. But MPAL has features of both, so the question of how best to treat patients with MPAL has been challenging the leukemia community worldwide—and long-term survival of patients has been poor," said Charles Mullighan, MBBS, MD, a member of the St. Jude Department of Pathology. He and Hiroto Inaba, MD, PhD, an associate member of the St. Jude Department of Oncology, are the study's corresponding authors. Long-term survival for young MPAL patients is 47-75 percent, compared to more than 90 percent for young ALL patients and 65-75 percent for AML.

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infusion, and second alloHCT are only successful in a minority of patients (*Haematologica* 2015;1222-1227). Recent advances involving pharmacologic agents including immunotherapies and small molecule inhibitors suggest that this approach may be an important new option for these patients.

Pharmacologic Immunotherapy

Therapies that stimulate engrafted donor-derived T cells to elicit a GVT effect have recently been explored to treat relapse after alloHCT. The interaction of the inhibitory immune checkpoint receptors CTLA-4 and PD-1 on donor-derived T cells with cognate ligands on tumor cells may help tumors evade the donor immune system. Monoclonal antibodies directed against CTLA-4 and PD-1 have substantial therapeutic activity in solid tumors, which provided an initial clinical experience that informed the trial design of these agents in the post-alloHCT setting.

CTLA-4 blockade was the first such approach evaluated specifically in the post-alloHCT setting. In a pilot phase I study for patients with relapsed hematologic malignances after alloHCT, low dose-ipilimumab (0.1-3.0 mg/kg) did not incite clinically significant GVHD but did have modest activity in three patients with lymphoid malignancies (*Blood* 2009;1581-1588).

A subsequent phase I/Ib multicenter study was conducted with ipilimumab dosed at 3 mg/kg or 10 mg/kg every 3 weeks for induction, with maintenance therapy offered every 3 months for up to a year in those with stable disease or better (*N Engl J Med* 2016;143-153). At the highest dose cohort of 10 mg/kg, seven of 22 patients (32%) had objective clinical responses with five CRs among patients with MDS and AML and two PRs among patients with multiple myeloma and Hodgkin lymphoma. GVHD was observed in four of 28 patients (14%) and was responsive to corticosteroids. Immune-related adverse events were observed in six of 28 patients (21%), and in one instance was fatal. Exploratory correlative studies showed a reduction in the number of circulating $CD4^+$ regulatory T cells with an increased conventional and $CD62L^-$ effector memory T cell populations. Increased CD8A and perforin expression was seen in gene expression and corresponding IHC analysis among responders.

A strong rationale also exists to explore PD-1 blockade in the post-alloHCT population. In particular, Hodgkin lymphoma and primary mediastinal B-cell lymphoma often feature 9p24.1 amplification, which is a disease-specific alteration that increases the gene dosage of PD-1 ligands, making them therapeutic targets of PD-1 inhibitors (*Blood* 2010; 3268-3277). PD-1 inhibitors are highly active and generally well-tolerated in relapsed or refractory Hodgkin lymphoma, and are now FDA-approved in that setting (*N Engl J Med* 2015;311-319; *J Clin Oncol* 2016;3733-3739).

However, the safety and efficacy of PD-1 blockade in the post-transplant setting remain unknown. Two important retrospective studies suggested that, although PD-1 blockade may be active for patients with Hodgkin lymphoma who relapse post-alloHCT, frequent GVHD may also be observed. In a French study, GVHD was observed in six of 20 cases (30%) though notably all six of these cases had prior history of acute GVHD (*Blood* 2017;2471-2478), while in a U.S. study, there were 17 of 31 patients with GVHD (55%) of whom several were steroid refractory and fatal (eight of 17 cases, 47%) (*Blood* 2017;221-228).

In myeloid malignancies, the results of PD-1 blockade post-alloHCT have been reported anecdotally in three patients, with evidence of one durable complete remission (though with GVHD) (*Bone Marrow Transplant* 2017;317-320). The responder had an increase in $CD3^+$ T-cell infiltration in the bone marrow 4 weeks after nivolumab. Further assessment of the safety and efficacy of this approach is needed in the context of prospective clinical trials. Three such studies in this population are currently underway to address this, including a phase I study evaluating lower doses of nivolumab across a broad range of hematologic malignancies (NCT01822509), a phase II pilot study with nivolumab (NIVALLO, NCT03146468), and a pilot study with pembrolizumab (NCT02981914).

Combination strategies in the post-transplantation setting to enhance the activity of checkpoint blockade are also underway. For example, a phase II clinical trial of 17 patients (10 allogeneic and seven autologous transplant patients) tested the combination of lenalidomide 10 mg daily for 21 out of 28 days with ipilimumab at 3 mg/kg administered every 28 days. Four of 10 post-alloHCT patients achieved durable CRs and three had PRs. Immune-related adverse events were observed in one patient with asymptomatic hypothyroidism and two patients with dermatitis. GVHD was observed in one post-alloHCT patient (*Clin Cancer Res* 2018;1011-1018).

Preclinical data suggest that epigenetic therapies may also be promising partners to checkpoint inhibitors. In addition to inducing cytotoxic $CD8^+$ T-cell activation, epigenetic therapies may sensitize tumors to subsequent immunotherapeutic strategies by increasing the "visibility" of leukemia cells to the immune system by induction of tumor antigen expression. A prospective clinical trial is evaluating the safety of decitabine priming prior to ipilimumab in patients with MDS and AML who are either post-alloHCT or transplant-naïve (NCT02890329).

Tyrosine Kinase Inhibitors

Targeted therapies may offer another opportunity to promote GVT without inducing GVHD. *FLT3*-mutated AML is associated with high relapse rates with standard chemotherapy and in the post-alloHCT setting. The addition of tyrosine kinase inhibitors (TKIs) such as midostaurin have improved overall survival for patients with AML with activated *FLT3* mutations (*N Engl J Med* 2017;454-464).

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Learning Objectives for This Month's CME Activity: After participating in this CME activity, readers should be better able to: 1. Identify new pharmacologic immunotherapy agents used in the treatment of relapsed hematologic malignancies after alloHCT transplantation. 2. Examine potential adverse and serologic effects of immune checkpoint inhibitors and tyrosine kinase inhibitors.

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Sorafenib is another oral multikinase inhibitor and is approved for the treatment of metastatic renal cell and advanced hepatocellular carcinoma. One of sorafenib's targets is *FLT3*-ITD, and maintenance sorafenib for patients with *FLT3*-ITD mutated AML is safe in the post-transplant setting, with comparable rates of GVHD to historical experience and promising clinical activity (1-year overall survival was 100%; only one of the 22 patients relapsed at 1 year) (*Biol Blood Marrow Transplant* 2014;2042-2048). Although the mechanism of sorafenib activity includes direct cytotoxicity, sorafenib also has indirect immune-mediated activity by reducing ATF4 levels, thereby inducing IL-15 production by increasing IRF-7 activation in *FLT3*-ITD+ leukemia cells (*Nat Med* 2018;282-291). Sorafenib's activity in the post-alloHCT setting may be due to leveraging the allogeneic $CD8^+$ T-cell response, which has the potential to lead to durable remissions. A more selective FLT3 inhibitor, gilteritinib, is under investigation in a large randomized trial as maintenance therapy in the post-alloHCT setting (NCT02997202).

BCR-ABL inhibitors in the post-alloHCT setting are safe and active at reducing the risk of relapse in patients with Philadelphia chromosome-positive (Ph+) leukemia (*Blood* 2007;2791-2793; *Blood* 2017;1170-1172). The use of alloHCT is now limited to the highest risk Ph+ leukemias, including those with chronic-phase CML who present in accelerated or blast crisis, and those with Ph+ acute lymphoblastic leukemia in first remission. Given the feasibility and observed benefit of adding a TKI in the post-alloHCT setting for this high-risk population, maintenance therapy with a TKI has been widely adopted, despite the lack of a randomized study.

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Conclusions

Tipping the scales toward GVT and away from GVHD remains the overall goal of immune-based approaches to treating hematologic malignancies that relapse after alloHCT. Monoclonal antibodies targeting immune checkpoints and targeted therapies such as TKIs have demonstrated efficacy in this challenging population, though more data are still needed to better understand how to improve the outcomes for patients treated with these approaches.

Tipping the scales toward GVT and away from GVHD remains the overall goal of immune-based approaches to treating hematologic malignancies that relapse after alloHCT.

Open questions include the optimal timing of deploying such therapies, developing predictive biomarkers of response and toxicity, and identifying optimal combination partners. With several studies now underway to answer these questions, in a short time we may be able to optimize the use of such approaches, which will ultimately benefit a greater number of patients with hematologic malignancies faced with this challenging situation of post-alloHCT relapse. OT