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FRONTLINE

A LYMPHOMA ROUNDS PUBLICATION

Fall 2016 Issue 4

IN THIS ISSUE

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Frontline is a Lymphoma Research Foundation (LRF) publication that features selected case presentations from LRF's ***Lymphoma Rounds*** professional education program, which provides a forum for local lymphoma healthcare professionals to meet on a regular basis to discuss actual lymphoma cases in a collaborative environment. ***Lymphoma Rounds*** is currently held in six U.S. cities with participation of over 40 academic and community centers.

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Optimizing Therapeutic Approaches in NK/T-Cell Lymphomas

Presenters

Matko Kalac, MD, PhD, *Columbia University Medical Center*
Karthik Ganapathi, MD, PhD, *Columbia University Medical Center*
Owen O'Connor, MD, PhD, *Columbia University Medical Center*

Dr. Owen O'Connor and Dr. Matko Kalac discussing their case at New York Lymphoma Rounds

In his discussion of NK/T-cell lymphomas, Matko Kalac, MD, PhD, of Columbia University Medical Center, presented two different cases of rare NK/T-cell lymphoma: one with a 'more typical' presentation and one less common presentation, each requiring consideration of different factors before identifying the best treatment approach.

Case Background

The first case involved a 40-year-old male with no past medical history who presented in May 2015 with a sore throat and cervical lymphadenopathy. He was prescribed valacyclovir and levofloxacin, which resolved the sore throat but not the lymphadenopathy. His family history revealed no history of malignancy. He had no notable social history, medications, or allergies.

The second case involved a 70-year-old man with a history of lower back pain, osteoarthritis, erectile dysfunction, hypertension, depression, and dyslipidemia. In March 2015 he presented with swelling of the right testicle. His family history included a mother with colon cancer at age 46. He had no notable social history.

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Medications included low-dose aspirin, atenolol, pravastatin, silodosin, valsartan/HCTZ, ezetimibe, and zolpidem. He had no known drug allergies.

Diagnosis

On exam the first patient was found to have palpable submandibular and bilateral non-tender, superficial cervical lymphadenopathy. He had no organomegaly and his exam was otherwise normal. His body mass index (BMI) was 20.6 kg/m^2. Notable laboratory findings included mild anemia, an elevated lactate dehydrogenase (LDH) (232 U/L), and EBV positivity (7741 IU/mL). A CT scan of the neck, chest, and abdomen confirmed bilateral cervical lymphadenopathy and generalized prominence of the lymphoid tissue in the hypopharynx. No enlarged mediastinal or abdominal lymph nodes were identified. An ear, nose, and throat (ENT) exam reported bogginess of the nasopharynx. A PET/CT scan showed active disease on both sides of the neck and some linear activity posterior to the nasopharynx that was attributed to the longus colli muscle (Fig. 1).

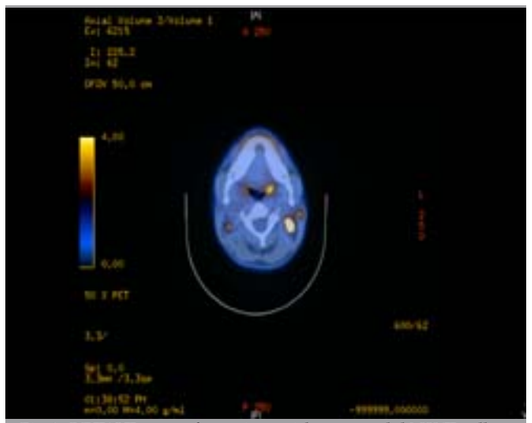

Fig.1. PET/CT scan of a patient with extranodal NK/T-cell lymphoma shows metabolically active disease present on both sides of the neck (maximum SUV, 11)

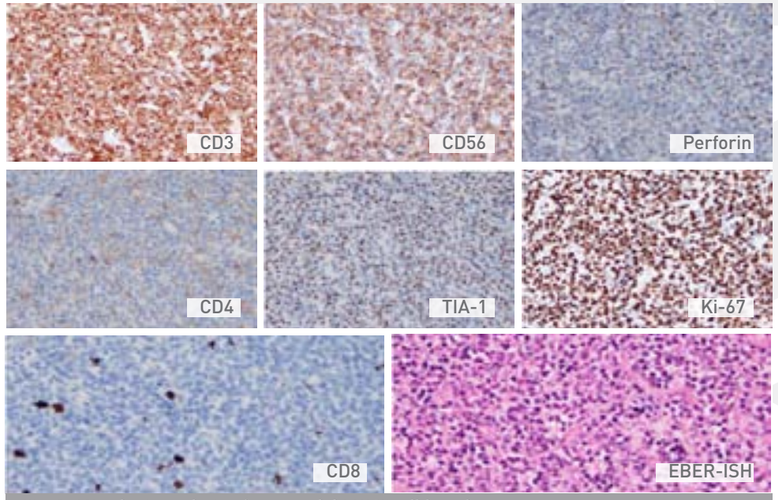

Fig. 2. Histologic analysis of extranodal NK/T-cell lymphoma

Karthik Ganapathi, MD, PhD, of Columbia University reviewed the pathology. A random nasopharyngeal biopsy from the first patient showed multiple fragments of predominately necrotic tissue. Focal areas were viable and revealed an atypical lymphoid infiltrate composed of medium to rare large cells with irregular nuclei, mature chromatin, inconspicuous nucleoli and minimal cytoplasm. These atypical cells were positive for by CD3, CD56, TIA1, granzyme B (variable), perforin (minority) and EBER-ISH.

The second patient underwent a testicular ultrasound that revealed a large hypoechoic mass with detectable vascularity. The left testicle was normal. His physical exam was otherwise normal with no organomegaly and no notable laboratory findings. Histologic analysis of excised testicle showed a diffuse atypical proliferation of medium-sized mature cells with irregular nuclei and inconspicuous nucleoli. Although this type of presentation in an older male is often first thought to be diffuse large B-cell lymphoma (DLBCL), the immunoblastic or centroblastic morphology typical of DLBCL was not present. However, there was substantial angioinvasion that is characteristic of NK/T-cell lymphoma. The sample was surface CD3-negative (CD3-positive in the cytoplasm), CD56-positive, CD4-negative, CD8-negative, TIA-1-positive, perforin-positive, granzyme B-positive, and EBV-positive with a high proliferative index (Fig. 2).

Both patients were diagnosed with extranodal NK/T-cell lymphoma.

Case Evolution

The first patient received 2 cycles of GELOX (gemcitabine, l-asparaginase, oxaliplatin) and attained a complete response. He is planned to have radiotherapy to the neck area (56 Gy total) and subsequently receive an additional 2 cycles of GELOX.

The second patient underwent right orchiectomy, which was followed by treatment using the SMILE regimen (methotrexate, leucovorin, ifosfamide, mesna, dexamethasone, etoposide, and L-asparaginase) for 3 cycles followed by 30

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Optimizing Therapeutic Approaches in NK/T-Cell Lymphomas

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Gy of radiotherapy to the left testicle in 10 fractions. A PET/CT scan at 3 months post-treatment showed a complete response.

Discussion

NK/T-cell lymphomas are predominately extranodal EBV-associated lymphomas that are uncommon in the U.S. and Europe and have a higher incidence in Asia and Latin America. They most often occur in the nose and upper aerodigestive tract but can occur in other sites, including the skin, gastrointestinal tract, testes, and bone marrow.

NK/T-cell lymphomas that present without an apparent nasal primary tumor were previously referred to as "nonnasal." However, it is now understood that these tumors are frequently associated with occult nasal primary tumors. It is important to confirm the NK/T-cell lymphoma diagnosis using either PET/CT scans and/or random punch biopsies of the nasopharynx in patients with an "extranasal" diagnosis and no evidence of disease on visual inpection of nasopharynx.

Many prognostic models have been used to risk stratify patients with NK/T-cell lymphomas, including the International Prognostic Index and the Italian Prognostic Index for PTCL-U (PIT), the International Peripheral T-cell Lymphoma Project (IPTCLP), which have been considered suboptimal. The Korean Prognostic Index, which was developed primarily in an Asian population, appears to have better prognostic value. The index includes LDH level, regional lymph node involvement, B-symptoms, and Ann Arbor stage. More recently, Dr. Seok Jin Kim and colleagues reported on the PINK and PINK-E prognostic indices. These models appear to correlate even better in this specific patient population. PINK-E is important because it incorporates EBV positivity, which was found to be an independent prognostic factor for overall survival.

Radiation therapy has an important role in the management of localized NK/T-cell lymphoma; however, it alone appears to be insufficient for attaining long-term disease control. The dose administered and the extent of the field are important parameters in assessing the overall efficacy of radiation therapy in this disease. Inclusion of all sinuses and the nasopharynx, as opposed to targeting only the primary lesions, has been associated with lower local relapse rates.

Although there are several effective systemic therapies for the disease, it is clear that CHOP is not an effective regimen for patients with NK/T-cell lymphomas. A variety of newer regimens have demonstrated marked activity. The SMILE regimen has demonstrated efficacy and is now commonly recommended, albeit, the regimen is associated with significant toxicity. The DeVIC regimen (dexamethasone, etoposide, ifosfamide and carboplatin), administered at two-thirds of the initially reported dose, has also demonstrated efficacy in combination with radiation therapy and appears less

Dr. Straus, Steering Committee chair, at New York Lymphoma Rounds

toxic than SMILE, though the concurrent radiation therapy is associated with substantial mucositis and poor oral intake for weeks after completion of therapy. More recently, the GELOX regimen (gemcitabine, oxaliplatin, and L-asparaginase) has demonstrated high response rates in combination with sequential radiation therapy in patients with early-stage extranodal NK/T-cell lymphoma.

The NK/T-cell lymphomas are a rare group of lymphoid malignancies that require a true multimodality approach involving highly specialized hematopathologists, radiation oncologists, radiologists, and medical oncologists. The focus of many of the emerging treatment algorithms is to reduce the substantial toxicity and co-morbidities associated with concurrent or sequential radiotherapy, while simultaneously improving long-term disease control. With the right tailored approach, most patients can expect a successful treatment outcome. ■

Mantle Cell Lymphoma Post-Ibrutinib

Presenter

Jeffrey Barnes, MD, PhD

Massachusetts General Hospital Cancer Center/Harvard Medical School

Case Background

In 2010, a 63-year-old man presented with lymphocytosis, thrombocytopenia, and splenomegaly. He was referred to hematology.

Diagnosis

A bone marrow analysis of the bone marrow suggested infiltration by a CD5-positive, CD20-positive, cyclin D1-positive lymphocytic infiltrate. Ki-67 and SOX11 expression was not yet available at that time. Based on the clinical and laboratory findings, he was diagnosed with mantle cell lymphoma (MCL).

Case Evolution

The patient received initial therapy with the Nordic regimen of dose-intensified induction immunochemotherapy with rituximab plus cyclophosphamide, vincristine, doxorubicin, and prednisone (Rmaxi-CHOP) alternating with high-dose cytarabine, followed by high-dose chemotherapy with BEAM (carmustine, etoposide, cytarabine, and melphalan) with rituximab in vivo-purged autologous stem cell transplant (ASCT).

Five years later, at age 68, the patient presented with leukocytosis. He was seen at an outside institution where clinicians were concerned that he had developed treatment-related acute myeloid leukemia (AML). However, a review of the peripheral blood smear indicated that the atypical lymphocytes with blast features were consistent with MCL blasts. At this time, his absolute lymphocyte count was 97,000 cells/mm^3, hematocrit was 27, and platelet count was 44,000 cells/mm^3. His performance status was excellent.

There was concern that the patient could have a blastoid variant that would not respond well to many therapies. The patient was not interested in an allogeneic transplant.

He received ibrutinib and developed the expected lymphocytosis, which subsequently resolved. For 6 months, he felt good and had normal blood counts. However, he then developed a relapse with a WBC of 20,000 cells/mm^3, no detectable neutrophils, a hematocrit of 20, and a platelet count of 6,000 cells/mm^3.

The patient then enrolled onto a trial of a CD20-targeting bispecific T-cell-engaging (BITE) antibody. His WBC count was 30,000 cells/mm^3 with no neutrophils and a platelet count of 6,000 cells/mm^3. He had diffuse bone marrow involvement and an enlarged spleen. The BITE antibody induced a dramatic response with resolution of most bone marrow disease and normalization of blood cell counts (Fig. 3). The patient developed severe cytokine release syndrome with tumor lysis requiring multiple doses of tocilizumab. After 4 weeks, he had progression of cutaneous lesions (Fig. 4). A second induction course of the BITE antibody was not effective and the patient developed disease progression with multiple cutaneous tumors, including some large lesions (> 20 cm). At this time, his WBC was 5 cells/mm^3, he was no longer transfusion-dependent, and his platelet count was approximately 120,000 cells/mm^3.

He was given 1 cycle of dose-reduced bendamustine/rituximab. The regimen induced a transient response in the cutaneous tumors but the tumors recurred before the next cycle. T-cells have been isolated from the patient in preparation for chimeric antigen receptor (CAR) T-cell therapy. During the waiting period, the patient received subcutaneous bortezomib. His CAR T-cell infusion is forthcoming.

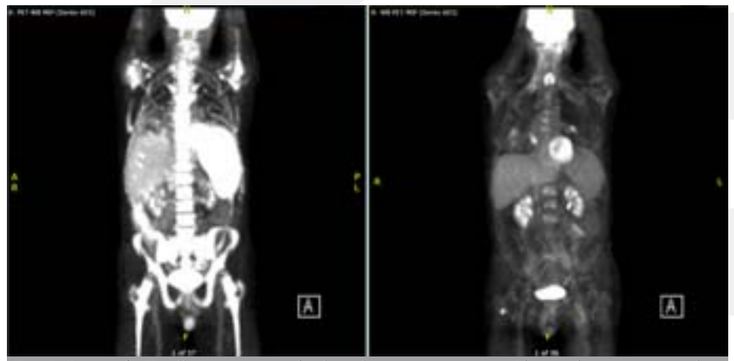

Fig. 3. Bispecific T-cell-engaging antibody induces response post-Ibrutinib in patient with MCL

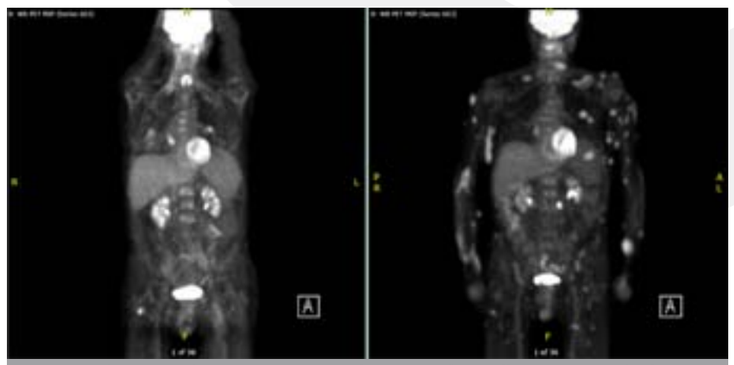

Fig. 4. Development of cutaneous tumors after Bispecific T-cell-engaging antibody in patient with MCL

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Mantle Cell Lymphoma Post-Ibrutinib

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Dr. Jeffrey Barnes presenting at New England Lymphoma Rounds

Discussion

Faculty discussed various aspects in the treatment of MCL, starting with the selection of initial therapy. Evidence suggests that some patients with MCL may have a long natural history and do not require immediate therapy. MCL in these patients is typically Ig-hypermutated and SOX11-negative. For patients requiring therapy, available regimens vary based on transplant eligibility. For transplant-eligible patients, an intensive cytarabine-containing regimen followed by ASCT is appropriate. Other initial combination regimens could include rituximab plus bendamustine, R-CHOP, or VR-CAP, which is the R-CHOP regimen but with bortezomib substituting for vincristine.[1]

For patients not eligible for transplant, options to consider include R-CHOP followed by maintenance rituximab and bendamustine/rituximab. Although many patients not eligible for transplant are also not candidates for R-CHOP, there are circumstances in which a patient ineligible for ASCT could receive R-CHOP. However, the randomized, phase III German Stil trial showed the superiority of bendamustine/rituximab versus R-CHOP in patients with MCL.[2] The role of rituximab maintenance therapy after R-CHOP in older patients was established in the European MCL Randomized trial, which demonstrated a survival improvement with rituximab over interferon.[3] The role of rituximab maintenance after bendamustine is unclear.

Outcomes tend to be poor for patients with blastoid variants. For a patient who has already received cytarabine-based therapy, ASCT, and ibrutinib, options to consider could be rituximab/bendamustine, VR-CAP, lenalidomide, bortezomib, or a clinical trial of a novel agent such as immunotherapy. Cytopenias could limit the use of some options such as lenalidomide as well as enrollment in some trials. However, trials for some immunotherapies, such as the BITE antibody trial in which the patient enrolled, have no hematologic requirements. ■

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Primary Gastric Lymphoma

Presenters

Colin Godwin MD, *Fred Hutchinson Cancer Research Center/ University of Washington*

Kristin Mantei, MD, MHA
CellNetix Pathology and Laboratories/ Swedish Medical Center

Nehal Masood, MD, MBBS
Multi-Care Tacoma

Case Background

A 57-year-old man developed occasional night sweats, some daytime fevers, and weight loss. He attributed the weight loss to poor appetite and dysphagia. Past medical history included diabetes mellitus, chronic obstructive pulmonary disease, hyperlipidemia, hypertension, and pulmonary vascular disease. He reported no remarkable family history. He was a long-time smoker and reported occasional alcohol use. The patient was referred to gastroenterology for evaluation.

Diagnosis

An upper endoscopy showed multiple ulcers. Analysis of a biopsy showed atypical infiltrating cells throughout the tissue sample. Infiltrating cells were large, irregularly shaped, CD20-positive and Ki-67-high (~95%), consistent with diffuse large B-cell lymphoma (DLBCL). Additional staining showed the infiltrate was CD10-negative, Bcl-6-positive, and strongly MUM1-positive, consistent with an activated B-cell (ABC)-like DLBCL. Although the cells had high c-Myc protein expression, no Myc translocation was detected by fluorescence in situ hybridization (FISH). However, a Bcl-6 translocation was observed.

A PET/CT scan showed intense uptake in the stomach, in lymph nodes in the neck, chest, and abdomen, and in areas of the small intestines. A staging bone marrow biopsy showed no lymphoma involvement. The patient was diagnosed with gastric DLBCL, stage IIIE or IV (depending on the staging system).

Case Evolution

The patient started chemotherapy with standard rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP), which was well tolerated aside from mild gastrointestinal toxicity and a self-limiting episode of shortness of breath. *H. pylori* eradication therapy was not administered, as its benefit is unclear in patients such as the case patient with lymph node involvement both above and below the diaphragm.

A restaging PET/CT scan after 4 cycles of therapy showed a complete metabolic response (Fig. 5). The patient completed 6 cycles of R-CHOP. He was referred to radiation oncology for consolidative radiation and received 36 Gy in 20 fractions to the site of initial bulky disease in the stomach. Radiation therapy was well tolerated. The patient remained in remission 6 months after completing treatment.

Discussion

Primary gastric lymphomas account for 20-30 percent of extranodal non-Hodgkin's lymphomas. The two most common gastric lymphoma subtypes are DLBCL and

Dr. Kristin Mantei presenting pathology at Seattle Lymphoma Rounds

mucosa-associated lymphoid tissue (MALT) lymphoma. Both can both be associated with *H. pylori* infection; thus, eradication therapy is a standard component of primary gastric lymphoma treatment. The role of eradication therapy in patients with systemic disease with gastric involvement is less clear.

Aggressive lymphomas with primary lesions located in the stomach are less likely than others to cause disseminated disease but are still associated with a worse prognosis.

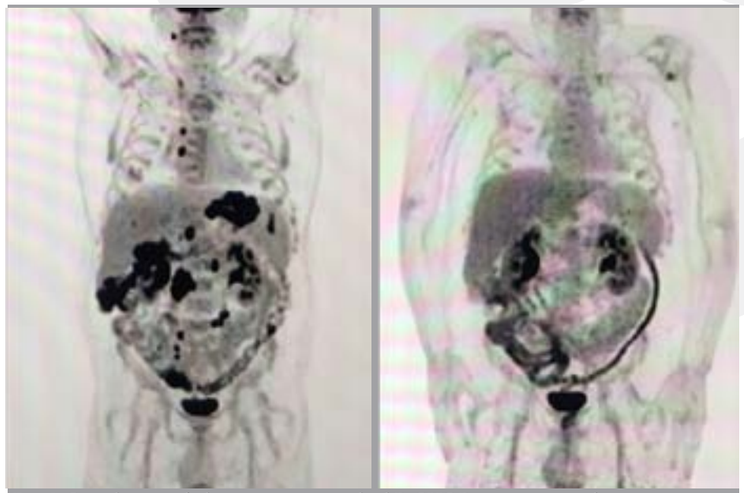

Fig. 5. Complete metabolic response to standard R-CHOP in a patient with primary gastric DLBCL

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Primary Gastric Lymphoma

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Some biomarkers, including MUM1, provide prognostic information but are not yet used to make treatment decisions.

Despite the increasing use of PET/CT scanning in patients with lymphoma, bone marrow biopsies remain an important diagnostic tool. A bone marrow biopsy was considered to be appropriate for the case patient, given his high probability of having bone marrow involvement, which is associated with an increased risk for CNS disease.

Staging of primary gastrointestinal lymphomas can be challenging, as the patterns of spread often differ from those observed with lymph node-based lymphomas. Multiple staging systems have been proposed, including modified Lugano staging, modified Ann Arbor staging, and the Paris TNMB classification. Few studies have directly compared these systems in patients treated with chemotherapy.

In terms of the initial treatment of primary gastric lymphoma, the current approach consists of combination chemotherapy. Surgery may have a role in selected patients, including those with bleeding or with perforation (although the risk of perforation is high in general in this population).

The use of intrathecal CNS prophylaxis in patients with DLBCL remains an area of debate. Bone marrow involvement, high lactate dehydrogenase (LDH), and older age have been identified as potential factors supporting the use of CNS prophylaxis. For the case patient, at 57 years of age with no detectable bone marrow involvement, some attendees suggested there was no clear evidence supporting the use of CNS prophylaxis whereas others thought it should be used, given that the potential benefit of preventing CNS disease would outweigh the risks.

The role of consolidation radiation therapy after initial chemotherapy is another point of consideration in patients with gastric lymphoma. National Comprehensive Cancer Network (NCCN) guidelines recommend considering radiation therapy in patients with initially bulky disease.[1] Clinical trials have demonstrated the safety of consolidative radiation therapy and retrospective studies have shown improved local control rates with its use. Moreover, in patients with DLBCL, advanced-stage disease tends to recur at sites of initial bulky disease. However, the role of consolidation radiation in patients with gastric lymphomas has not been well studied prospectively, particularly in the rituximab era. ■

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Researcher Spotlight

David Scott, MBChB, PhD

Correlative studies are crucial to a full understanding of how a given therapy impacts patient outcomes. However, funding for clinical trials often does not extend to supporting correlative studies conducted after the trial concludes. The Lymphoma Research Foundation's 2016 Mantle Cell Lymphoma Correlative Studies Support Initiative was designed to support such a correlative project in mantle cell lymphoma (MCL). "This funding mechanism fills a large gap in patient-oriented research," says Brad Kahl, MD, of Washington University in Saint Louis and Chair of the Foundation's MCL Consortium. The one-year award was granted to David Scott, MBChB, PhD, of the British Columbia Cancer Agency in Vancouver, Canada.

Dr. Scott's project seeks to address the difficulty in identifying which MCL patients respond well to treatment and which have a more aggressive form of MCL that responds poorly to even the most aggressive therapies. "We have recently developed a new test that measures the 'proliferation signature' – how quickly the MCL cells are multiplying – and this tightly relates to how long the lymphoma is controlled by standard treatment," Dr. Scott explains. "In this project, we will apply this test to tissue biopsies from patients treated with the most intensive treatments currently being used in this disease. This will allow us to see whether these intensive treatments improve outcomes for those patients at highest risk of early relapse."

Dr. Scott and his colleagues will use their proliferation signature test on biopsies from the Alliance 50403 trial, in which patients received intensive treatments followed by maintenance or consolidation with bortezomib, to demonstrate that the test works as a predictor of outcome in patients treated with the most intensive regimens. "The next step is to show that you can alter the outcomes for patients at high risk of early relapse by changing their treatment," he notes.

Dr. Scott, who also received the Foundation's Adolescent/Young Adult Lymphoma Correlative Studies Award in 2015, is a clinician-scientist at the British Columbia (BC) Cancer Agency and an Assistant Professor at the University of British Columbia. Dr. Scott's current research focuses on translating discoveries about the biology of lymphoma into tools that can be used in the clinic; he notes that funding from the Lymphoma Research Foundation "has been critical to my research in laying the foundation for precision medicine through the use of molecular tests."

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