Case Background
A 34-year-old woman previously diagnosed with grade 2 follicular lymphoma had already received 10 prior lines of therapy, including various combination chemotherapy regimens with or without rituximab; ibrutinib; allogeneic bone marrow transplant; lenalidomide/rituximab; and ibrutinib. Her therapy prior to enrolling on the CART 19 T-cell trial was carboplatin/gemcitabine, which had achieved stable disease for several months.

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CAR T-Cell Therapy to Treat Double Hit Lymphoma

Continued from page 1

Case Evolution

In 2015, the patient enrolled onto the clinical trial of CART19 T-cells in relapsed/refractory CD19+ non-Hodgkin lymphoma (NHL). She first received carboplatin/gemcitabine as lymphodepleting chemotherapy and, 9 days later, received an infusion of her CAR T-cells that had been previously isolated and modified to recognize the tumor B-cell antigen CD19. Dr. Schuster observed that, because the patient had previously received an allogeneic transplant and had 100% chimerism, the transduced T-cells were all donor-derived cells. These donor-derived T-cells did not induce a graft-versus-host disease upon reinfusion, perhaps because of prior immunologic tolerance. Initially, the patient appeared to benefit following CART T-cell therapy, as a large palpable abdominal mass appeared to gradually decrease in size and the patient reported feeling good. However, less than 3 months after the CAR T-cell infusion, clinical progression of disease was evident.

Megan Lim, MD, PhD, also of the University of Pennsylvania, discussed the pathology of the case. She noted that a biopsy of the abdominal mass taken on Day +78 post-CAR T-cell infusion showed CD10+, CD19+, kappa light chain-restricted large malignant cells (Fig. 1A). Immunohistochemistry revealed large PAX5+, PDL1+ B-cells. Fluorescence in situ hybridization (FISH) was positive for c-MYC and BCL-2 rearrangements, indicating transformation from follicular lymphoma to double-hit diffuse large B-cell lymphoma (DLBCL).

The patient next received two doses of radiation therapy followed by two doses of the checkpoint inhibitor nivolumab. Dr. Schuster explained that the aim of nivolumab was to stimulate the CAR T-cells. The patient received doses of nivolumab on November 19 and December 9; by December 30, a PET/CT scan showed that the large tumor now had minimal residual FDG uptake with significant necrosis (Fig. 1B).

Several months later, the patient developed abdominal pain; a CT scan showed intestinal perforation. The patient was taken into surgery, where the abdominal mass, which had involved the bowel wall, was removed along with several ovarian metastases. Pathologic analysis of the mass revealed only necrotic tissue (Fig. 1B). The patient remains in complete remission by imaging 15 months following her second round of nivolumab.

Fig. 1A & R. FL Transformed to “Double Hit” DLBCL

FL Transformed to “Double Hit” DLBCL

A. October 15, 2015: Day + 78 CTL019.


Biopsy: October 23, 2015

• Flow: kappa LC, CD10+, CD19+
• HIC: large PAX5+ B cells; PDL1+
• FISH: c-MYC and BCL-2 rearranged

Biopsy: March 6, 2016

• Extensive necrosis
• No tumor seen

Dr. Stephen Schuster, Philadelphia Lymphoma Rounds Steering Committee Chair

Discussion

Dr. Schuster proposed that in some patients, CAR T-cells appear to be recognizing tumor antigen but are being “turned off” by the tumor. However, the case he presented suggests that an immune checkpoint inhibitor may be able to reactivate these CAR T-cells enabling them to destroy tumor cells. Dr. Schuster concluded that larger trials are in progress to further evaluate the role of CAR T-cells and the potential addition of immune checkpoint modulation, in double-hit lymphomas.

Foundation Releases New Immunotherapy Fact Sheet and Video

An essential hallmark of the Lymphoma Research Foundation is its ability to provide the lymphoma community with the latest information on lymphoma research and treatment through its highly-regarded patient education resources. The Foundation is proud to provide education resources covering the latest in cancer treatment—immunotherapy.

LRF’s new Immunotherapy Fact Sheet and YouTube video, introduce members of the lymphoma community to this treatment option and discuss how it can harness and enhance the innate powers of the immune system to fight cancer cells.

To download the free fact sheet, visit lymphoma.org/patienteducation; and visit LRF’s YouTube Channel (youtube.com/lymphomaresearch) to watch the Immunotherapy in Lymphoma video.

Continued on page 3
A Case of Sezary Syndrome

Case Background

The first case was a 61-year-old Caucasian woman with no significant past medical history presented to hematology with unexplained leukocytosis. More than a year prior, a dermatologist had diagnosed her with atopic dermatitis with generalized pruritus, redness, and dry skin.

The second case was a 70-year-old healthy Caucasian female who was referred to oncology after finding a lump in her groin shortly after a normal physical exam.

Diagnosis

The first patient presented with generalized pink skin (erythroderma) with mild scaling, mild swelling, and fine wrinkling of the truncal skin, and hyperlinear palms. An outside complete blood count (CBC) showed a white blood cell (WBC) count of 22.7 cells/μL with 69.5% lymphocytes.

The second patient was diagnosed with a dermatologist with a CD4:CD8 ratio ≥ 10, or increased lymphocytes; novel markers such as the transcription factor TCF-7. The patient was started on FDA-approved therapy due to an inflammatory reaction, can be quite subtle. Patients have generalized lymphadenopathy, lymph nodes can be smaller, and with less intense FDG uptake, than observed in nodal lymphomas. Flow cytometry of peripheral blood and lymph nodes must include markers more specific for CTCL, such as CD2 expression on CD4+ cells. Dr. Geskin noted that the erythroderma, which is caused by an influx of red blood cells due to an inflammatory reaction, can be quite subtle. Patients have generalized lymphadenopathy, lymph nodes can be smaller, and with less intense FDG uptake, than observed in nodal lymphomas. Flow cytometry of peripheral blood and lymph nodes must include markers more specific for CTCL, such as CD2 expression on CD4+ cells. Novel markers such as the transcription factor TCF-7 are being developed to improve diagnosis.

Discussion

Sezary syndrome is characterized by clinical and laboratory features. The ISCL/EORTC criteria defines Sezary syndrome as having at least 1 of the following criteria: erythroderma; clonal TCR rearrangement; or an absolute malignant cell count > 1000 cells/mm³, increased CD4+ or CD3+ cells with a CD4:CD8 ratio > 10, or increased CD4+ cells with an abnormal phenotype. Dr. Geskin noted that the erythroderma, which is caused by an influx of red blood cells due to an inflammatory reaction, can be quite subtle. Patients have generalized lymphadenopathy, lymph nodes can be smaller, and with less intense FDG uptake, than observed in nodal lymphomas. Flow cytometry of peripheral blood and lymph nodes must include markers more specific for CTCL, such as CD2 expression on CD4+ cells. Novel markers such as the transcription factor TCF-7 are being developed to improve diagnosis.

Dr. Chadburn discussed the differential diagnosis of CD4+ T-cell lymphomas. She noted that reactive CD4+ peripheral blood lymphocytes can occur from a variety of causes but CD8+ cell numbers are sometimes also increased in these patients. Other potential causes of elevated CD8+ T-cell concentrations include recall/extranodal lymphoma of the usual histologic types, and with radiation therapy. A Case of Sezary Syndrome

Case Evolution

The first patient was initially treated with 6 cycles of cyclophosphamide, doxorubicin, vincristine, prednisone (CHOP) for presumed diagnosis of PTCL but relapsed within a month with more severe clinical symptoms, including itching that became so severe that the patient was unable to continue with daily activities. Repeat PET/CT scan showed progressive disease.

The patient was referred to Comprehensive Cutaneous Oncology Center at Columbia University to be evaluated by Dr. Geskin, a cutaneous lymphoma specialist. She underwent complete work up again, including peripheral blood flow cytometry, which specifically evaluated for loss of CD26 expression on CD4+ cells in the blood. The sample was found to have 90% of CD4+ cells without CD26 marker, indicating that almost the entire CD4+ population was malignant (Fig. 2A). The absolute count of CD4+CD26- cells was 1,800 cells/μL, which together with other clinical (erythroderma) and radiological findings (enlarged peripheral lymph nodes) confirmed the diagnosis of a cutaneous T-cell lymphoma (CTCL), Sezary syndrome with leukemic involvement based on the International Society for Cutaneous Lymphomas (ISCL) and European Organization of Research and Treatment of Cancer (EORTC) classification. The patient was started on FDA-approved therapy with romidepsin, which did improve her skin disease with significant improvement in her pruritus, but did not appear to yield a substantial benefit in the blood after 2 months of therapy. She then received low-dose alemtuzumab (3 mg 3 times/week with appropriate prophylaxis against infection) for 3 weeks (Renebrogan protocol), which led to a clearance of malignant cells from her blood and a normalization of the WBC count; she tolerated it well. Ten months out, she had no signs of disease. Her skin-directed therapy used to treat mild residual skin disease consisted only of topical nitrogen mustard gel.

The second patient was also referred to the Comprehensive Cutaneous Oncology Center at Columbia University to be evaluated by Dr. Geskin. Her peripheral blood flow cytometry analysis revealed 95% of CD4+ lymphocytes without CD26 expression, consistent with leukemia involvement per the ISCL/EORTC classification of Sezary syndrome (Fig. 2B). She had a good response to a low dose of the retinoid bexarotene, photopheresis and appropriate topical therapies. She remains asymptomatic after nearly a year.

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Dr. Larisa Geskin presenting at the National Lymphoma Rounds Summit

A Case of Sezary Syndrome

Continued from page 4

A. Patient 1

B. Patient 2.

Fig. 2A & B. Pathological analysis of two patients with Sezary syndrome

Continued on page 5
Waldenström’s Macroglobulinemia Non-Responsive to Ibrutinib

Dr. Jorge Castillo, MD
Dana-Farber Cancer Institute

Case Background
A 75-year-old man with a history of stage 2 rectal cancer treated with surgery and radiotherapy 4 years prior developed bright red blood per rectum (BRBPR) that was occurring at increasing frequency over 2 months. He also had progressive fatigue and pallor and a hemoglobin level of 4 g/dL. The gastrointestinal (GI) bleeding was attributed to hyperviscosity, which was caused by Waldenström’s macroglobulinemia (WM). The patient was hospitalized, given a transfusion, and evaluated with upper and lower endoscopies, which did not reveal a source of the bleeding.

Case Evolution
The patient started horizonzab, dexamethasone, and rituximab (HDR) as initial therapy, with bortezomib administered subcutaneously on a weekly schedule. He continued to undergo weekly plasmapheresis due to high IgM levels. His GI bleeding resolved. He tolerated the regimen without any major adverse events, although after 4 cycles no response was detected. Dr. Castillo noted that IgM flare could not be ruled out as biopsy was not performed at that time.

The patient went on to receive bendamustine and rituximab for 6 cycles, which induced a minor response with an IgM reduction of 40%. Plasmapheresis was stopped. However, within 6 months, the patient’s IgM level began increasing again and his GI bleeding returned.

Discussion
Dr. Castillo noted that in a patient with this type of presentation, the differential diagnosis includes Waldenström macroglobulinemia, IgM multiple myeloma (occurs rarely), and IgM-secreting lymphomas such as marginal zone lymphoma, follicular lymphoma, and small lymphocytic lymphoma. However, the high IgM level does suggest WM (lymphoplasmacytic lymphoma with an IgM monoclonal spike) rather than other lymphomas.

Imaging tests confirmed that there was no rectal cancer recurrence. The patient was prescribed ibrutinib 420 mg once daily which induced stable disease after 3 months, with an IgM reduction of 10%. Side effects were limited to minor bruising. He again required plasmapheresis due to BRBPR.

At this point, the patient was referred to a specialty center and underwent another bone marrow biopsy. Dr. Castillo explained that his center assesses MYD88 mutational status through PCR and next-generation sequencing of the bone marrow. If a sample does not test MYD88 mutation-positive by either method, then MYD88 gene sequencing is done, as other MYD88 mutations have been identified. All mutational testing was negative, indicating the patient had MYD88<sup>WT</sup> WM.

A follow-up bone marrow biopsy revealed PAX5 expression, which indicated a lymphocytic component, providing additional evidence that this was not multiple myeloma. Also, IgM myeloma is typically characterized by cyclin D1 expression, which was not expressed in this case. Clinically, common features of IgM myeloma include bone lesions, renal failure and hypercalcemia. The patient did not have any of these findings.

The patient next enrolled on a clinical trial of single-agent venetoclax. After 3 months, his IgM level had declined and he was able to stop plasmapheresis. He remains on treatment.

Presentation

Waldenström’s Macroglobulinemia Non-Responsive to Ibrutinib

Continued from page 6

WM is commonly associated with anemia but can also manifest as anemia and splenomegaly. IgM myeloma, cryoglobulinemia, cold agglutinemia, and hyperviscosity syndrome (eg, nosebleeds, headache, vision impairments). Although anemia in patients with WM is more often due to bone marrow replacement, it can also be caused by elevated hepcidin levels that result in poor iron absorption.

Dr. Castillo pointed out that not all patients with WM require treatment. Low hemoglobin or platelet levels, symptomatic hyperviscosity, moderate to severe peripheral neuropathy, symptomatic extramedullary disease, symptomatic cryoglobulins, cold agglutinins, autoimmune-related events, and amyloidosis are all indications for treatment.

For patients requiring treatment, options include combination chemotherapy (eg, cyclophosphamide, dexamethasone, and rituximab; bendamustine and rituximab; bortezomib, dexamethasone, and rituximab; carfilzomib, dexamethasome, and rituximab; and single-agent ibrutinib, which received U.S. Food and Drug Administration (FDA) approval in 2015 for use in WM. Dr. Castillo pointed out that the indication does not specify prior lines of therapy, although, clinical trial data are limited to previously treated patients. A clinical trial is underway evaluating ibrutinib in the front-line setting in patients with WM.

The mutational status of two genes—MYD88 and CXCR4—has been shown to correlate with responsiveness to ibrutinib in patients with WM. In 2015, Dr. Steven Treon and colleagues reported the best responses to ibrutinib in patients with the MYD88<sup>L265P</sup>/CXCR4<sup>WT</sup> genotype, followed by MYD88<sup>WT</sup>/CXCR4<sup>L265P</sup> and the poorest responses in patients with MYD88<sup>WT</sup>/CXCR4<sup>L265P</sup> overall response rate, 100%, 85.6%, and 60%, respectively; P < 0.001. Not only are response rates lower in the less favorable groups, but the depth of response is also lower (major response rate, 91.7%, 61.9%, and 0%, respectively; P < 0.001). [N Engl J Med 2015;373:584-586]. The MYD88<sup>L265P</sup>/CXCR4<sup>WT</sup> genotype is also associated with poor prognosis in patients with WM.

Based on these findings, genotyping is useful for patients with WM considering ibrutinib. Dr. Castillo noted that he does not administer ibrutinib to patients with MYD88<sup>WT</sup>/CXCR4<sup>L265P</sup> because of the low likelihood of benefit. Whether these mutations have predictive value for other therapies is currently unknown.

There are several therapeutic options for patients with ibrutinib-resistant WM; proteasome inhibitors, alkylating agents, monoclonal antibodies, nucleoside analogues, mTOR inhibitors, immunomodulating drugs, and autologous stem cell transplant have all shown activity in patients with WM. The BCL-2 antagonist venetoclax is currently being evaluated in a multicenter phase 2 trial in patients with relapsed/refractory WM.
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