Patient Case Studies and Panel Discussion: Leukemia – Rare and Emerging Subtypes

ABSTRACT

Rare and emerging subtypes of leukemia can be incredibly challenging to diagnose and even more challenging to treat. At the NCCN 2019 Annual Congress: Hematologic Malignancies, a panel of experts, moderated by Andrew D. Zelenetz, MD, PhD, were presented with particularly challenging cases in these malignancies and asked to discuss best approaches to treatment.

J Natl Compr Canc Netw 2019;17(11.5):1451–1453
doi: 10.6004/jnccn.2019.5029

Rare and emerging subtypes of leukemia can be incredibly challenging to diagnose and even more challenging to treat. At the NCCN 2019 Annual Congress: Hematologic Malignancies, a panel of experts, moderated by Andrew D. Zelenetz, MD, PhD, were presented with particularly challenging cases in these malignancies and asked to discuss best approaches to treatment.

Patient Case Study 1

In the first case study, a 77-year-old woman presented with multiple nodular lesions and plaques on her face, chest, and back. She had a history of type 2 diabetes, stage 3 hypertension, hyperlipidemia, coronary heart disease, cerebral infarction, glaucoma, lens extracapsular extraction and posterior chamber intraocular lens implantation, Sjögren syndrome, rheumatoid arthritis, and left axillary vein and brachial vein thrombosis.

She had previously received a conventional therapy of Chinese medicine, but her condition did not improve. Her clinicians performed a bone marrow biopsy and an aspiration biopsy of a nodule on the right side of her face, and immunostaining results revealed the following immunophenotype: CD4+, CD123+, CD43+, CD56+, with Ki-67 level of 30% to 40%.

The patient was diagnosed with blastic plasmacytoid dendritic cell neoplasm, which is a rare blood cancer in the myeloid malignancies family. Andrew D. Zelenetz, MD, PhD, Memorial Sloan Kettering Cancer Center, noted that this disease used to be classified as a variant of acute lymphoblastic leukemia (ALL) and has a distinctive immunophenotype and clinical appearance, characterized by purple skin lesions.

He said a helpful tool for remembering the immunophenotype of this disease is to think “123456”: CD123, CD4, and CD56. Conversely, Nitin Jain, MD, The

University of Texas MD Anderson Cancer Center, noted that although this rule of thumb can be helpful, it is important to keep in mind that approximately 10% of patients with this malignancy are actually CD56-negative.

Daniel A. Pollyea, MD, MS, University of Colorado Cancer Center, emphasized the unique phenotypic expression pattern in this malignancy, and the risk of cytopenias due to bone marrow involvement. “Certainly there are patients with bone marrow involvement who don’t have cytopenias and have predominant expression of these skin manifestations,” he said. “But I think the CD123 is really the key, because this is a very, very difficult diagnosis to make, and that can be the linchpin.” He added that CD123 expression status is important to know not only for diagnostic purposes but also from a therapeutic perspective. However, many clinical pathologists do not possess the capabilities to test for CD123, so if a diagnosis of blastic plasmacytoid dendritic cell neoplasm is even being entertained, a discussion with a pathologist regarding testing for CD123 is critical.

The nodule on the right side of the patient’s face was surgically excised, and she was treated with gemcitabine, nedaplatin (a second-generation platinum drug used in China that is not approved by the FDA; it is similar to carboplatin and cisplatin), and bleomycin. The patient experienced an initial response to therapy but subsequently developed additional nodular lesions on her arm.

According to Dr. Pollyea, regardless of what transpired with this particular patient, surgical resection of skin lesions did not have a role in this case. “Typically, if the disease is going to respond, the skin lesions are very, very sensitive,” he said. “So there are issues with wound healing if you perform a large resection.”

The panel then discussed tagraxofusp-erzs, a recently approved drug for the treatment of this disorder that has

been shown to be highly effective.¹ Dr. Pollyea noted that the mechanism of action of this drug is “quite brilliant.”

“You’re taking one of nature’s most potent toxins and delivering it directly to a cell population of critical importance in this disease, and potentially the precursor or primitive population of the disease,” he said.

A trial of tagraxofusp treatment in patients with blastic plasmacytoid dendritic cell neoplasms led to durable responses and high complete response rates, particularly in the first-line setting (72%).¹ In relapsed/refractory disease, it was less effective, but “still very effective,” according to Dr. Zelenetz, with a complete response rate of 38%. However, significant toxicity was seen, with capillary leak syndrome a fatal toxicity.

Jae Park, MD, Memorial Sloan Kettering Cancer Center, noted that because of the limited clinical experience with this agent, it is critical to administer the drug in an inpatient setting whenever possible and to closely monitor any patient-related physical changes, including weight fluctuations, kidney function, and respiratory status.

William G. Wierda, MD, PhD, The University of Texas MD Anderson Cancer Center, agreed, adding that he actually treated patients with this compound on a clinical trial before its approval. “During the trial, we were closely monitoring daily weight, albumin, and [liver function], and making daily adjustments in dosing based on what was happening with patients clinically,” he said. “So it’s important to be very familiar with the prescribing information.”

Given this particular patient’s age, history, and comorbidities, stem cell transplantation was not an option. However, according to Dr. Park, allotransplant should be considered in these cases whenever possible, and earlier rather than later. “Even with a good response, it becomes difficult to continue this regimen,” he said. “And after [patients] relapse, there are very few treatment options available.”

Patient Case Study 2

A 28-year-old woman presented with fatigue and lymphadenopathy. Her initial WBC count was 11.1 k/uL with 40% blasts, and she showed hypercellular bone marrow. Her immunophenotype included the following: 88.0% CD45+/-, CD34+, CD19+, CD10+ (variable), CD20- (~4% of cells stain), sCD22+, CD13-, CD33-, CD38+, CD56-, CD2+/-, CD3-, CD4-, CD8-, CD7-, CD5-, CD117, HLA-DR+, sIg light chain-, cCD79a+, cCD22+, MPO-, cIgM+, and TdT+. After noting the complexity of the patient’s immunophenotype, Dr. Pollyea emphasized the importance of working with a skilled hematopathologist in cases such as this.

The patient was diagnosed with B-cell ALL and treated with the CALGB 10403 regimen.² At day 30, bone

marrow biopsy showed residual disease with 16% blasts by flow. As her next course of treatment, the patient received blinatumomab for one cycle.

Dr. Jain agreed that this was a reasonable next step, but added that an additional cycle of chemotherapy would also have been feasible. Although the patient was high-risk, he would not yet say treatment had failed after only one treatment cycle.

“I think on the adult side we have to take our cues from the pediatricians who have been so incredibly successful with this disease,” said Dr. Pollyea. “And CALGB 10403 is a regimen that attempts to apply the pediatric regimens to an adolescent/young adult population.”²

He added that pediatricians tend to stick to protocol, and the protocol for this particular regimen allows for a more extended induction period. “So at this point you should have a lot of concerns about this patient, but I think the protocol allows you to continue.”

About 4 weeks after starting blinatumomab, the patient experienced complete remission confirmed by bone marrow biopsy. She also received 6 cycles of intrathecal chemotherapy throughout the course of her treatment and showed no evidence of central nervous system involvement.

A month later, she presented with enlarged lymph nodes in her groin and neck, and bone marrow biopsy confirmed 63% blasts with an ALL phenotype. A same-day inguinal lymph node biopsy was consistent with lymphoblastic leukemia involvement.

Although the patient experienced a complete remission initially, Dr. Park noted that minimal residual disease (MRD) status was never confirmed. This factor is critical in assessing a patient’s depth of remission, and MRD-positive patients should receive additional therapy sooner rather than later to get to MRD-negative status, he said.

Dr. Jain said that additional diagnostic testing in the form of RNA sequencing would be appropriate in this case, but noted a caveat of the limited availability of this type of testing. The patient underwent next-generation sequencing (NGS), which revealed the following: DIAPH1-PDGFRB fusion; CDKN2A/B - p14^{ARF} loss exon 1 and CDKN2b loss; PIK3R1 splice site 1746-2A>6; and TP53 N288fs*60.

According to Dr. Park, interpreting NGS data can be difficult, and misinterpretation can lead to the wrong choice of treatment. This again underlines the importance of consulting with a skilled pathologist or other experienced ALL expert to assist in interpreting mutation profiles.

The patient was determined to have Ph-like ALL (a newly recognized entity of Ph-negative ALL with a poor prognosis) and was enrolled in the KTE-CA19 CAR-T (axicabtagene ciloleucel [axi-cel]) trial (ClinicalTrials.gov

identifier: NCT02614066). She received cytoreductive chemotherapy with hyperCVAD part A before apheresis for CAR-T generation, and experienced favorable cytoreduction (she received fludarabine/cyclophosphamide for lymphodepletion). She then received a post-CAR-T infusion and showed no response; her blast count increased from 0.42 to 80.35 within a week.

“This is just a tough case,” said Dr. Park, noting the unusually refractory nature of the disease. “Initial response rates to CAR-T cell therapy are approximately 80%, so she’s already in the very unlucky 20% of cases,” he said.

Dr. Jain described 2 subtypes of Ph-like ALL: approximately half are *CRLF2*-rearranged,³ and these patients should ideally be referred to a clinical trial. The other half are nonrearranged,³ and these patients should be referred for RNA sequencing to determine fusion genes.

No response was seen to further treatment, and the patient chose to continue care in hospice.

According to Dr. Zelenetz, incorporation of comprehensive genetic analysis and fluorescence in situ hybridization testing is important to identify high-risk patients (such as those with Ph-like phenotype) and plan for allogeneic hematopoietic stem cell transplantation (alloHSCT) or referral to clinical trials as early as possible.

MRD assessment by flow and/or NGS is critical to assess depth of response, modification of therapy, and candidacy for early alloHSCT. Dr. Park noted that both gene sequencing tests are validated, so patient preference should take priority.

Incorporation of tyrosine kinase inhibitors (TKIs) in Ph-like ALL is being investigated in clinical trials, and patients with this disease should be referred earlier rather than later, added Dr. Zelenetz. “But the nuance to that is understanding how to integrate TKIs into this entity, which is going to be dependent on understanding the mechanisms involved in the disease,” he said. “It won’t be just one TKI [that everyone receives]; it’s much more complicated than that, unfortunately.”

Dr. Jain added that although Ph-like ALL has been established as high risk in the setting of chemotherapy, its classification remains to be determined in the new era of targeted therapies. “Some emerging data suggest that blinatumomab, inotuzumab, and CAR-T-cell therapy may overcome the negative prognostication of Ph-like ALL,” he said. “So those are some data we’ll hopefully see at the ASH Annual Meeting.”

Jarrod Holmes, MD, Annadel Medical Group, also participated in the panel discussion.

Disclosures: Dr. Zelenetz has disclosed that he receives research support from Genentech/Roche, Gilead, MEI, and BeiGene; he has been a consultant for Celgene/JUNO, Genentech/Roche, Gilead, BeiGene, Pharmacyclics, Janssen, Amgen, Astra-Zeneca, Novartis, and MEI Pharma; and he is on the Scientific Advisory Board of the Lymphoma Research Foundation and Adaptive Biotechnologies. Dr. Jain has disclosed that he is a consultant for AbbVie, Inc., AstraZeneca Pharmaceuticals LP, Genentech, Inc., Janssen Pharmaceutica Products, LP, Adaptive Biotechnologies, Precision Biosciences, Verastem, and Pharmacyclics; receives grant/research support from AbbVie, Inc., AstraZeneca Pharmaceuticals LP, Bristol-Myers Squibb Company, Genentech, Inc., Incyte Corporation, Adaptive Biotechnologies, ADC Therapeutics, Cellectis, Precision Biosciences, Servier, Verastem, Pfizer, Inc., and Pharmacyclics; is a scientific advisor for AbbVie, Inc., AstraZeneca Pharmaceuticals LP, Genentech, Inc., Janssen Pharmaceutica Products, LP, Adaptive Biotechnologies, Precision Biosciences, Verastem, and Pharmacyclics; and has received honoraria from AbbVie, Inc., AstraZeneca Pharmaceuticals LP, Genentech, Inc., Janssen Pharmaceutica Products, LP, Adaptive Biotechnologies, Precision Biosciences, Verastem, and Pharmacyclics. Dr. Park has disclosed that he receives grant/research support from Amgen Inc., Genentech, Inc., Incyte Corporation, Juno Therapeutics, Inc., Kite Pharma, Novartis Pharmaceuticals Corporation, and Servier; and is a scientific advisor for from Amgen Inc., AstraZeneca Pharmaceuticals LP, GlaxoSmithKline, Incyte Corporation, Kite Pharma, Novartis Pharmaceuticals Corporation, Allogene Therapeutics, Autolus Therapeutics plc, and Takeda Pharmaceuticals North America, Inc. Dr. Pollyea has disclosed that he is a scientific advisor for AbbVie, Inc., Agios, Inc., Celgene Corporation, Daiichi-Sankyo Co., Forty Seven, Inc., Janssen Pharmaceutica Products, LP, Pfizer Inc., and Takeda Pharmaceuticals North America, Inc. Dr. Wierda has disclosed that he is a consultant for Genzyme Corporation and receives grant/research support from AbbVie, Inc., Acerta Pharma, Genentech, Inc., Gilead Sciences, Inc., Janssen Pharmaceutica Products, LP, Juno Therapeutics, Inc., Karyopharm Therapeutics, Kite Pharma, Cyclacel Pharmaceuticals, Inc., GlaxoSmithKline/Novartis Pharmaceuticals Corporation, Loxo Oncology, Inc., miRagen Therapeutics, Inc., Oncternal Therapeutics, Inc., Xencor, Inc., Pharmacyclics, and Sunesis Pharmaceuticals, Inc. Dr. Holmes has disclosed that he has no financial interests, arrangements, affiliations, or commercial interests with the manufacturers of any products discussed in this article or their competitors.

References

1. Pemmaraju N, Lane AA, Sweet KL, et al. Tagraxofusp in blastic plasmacytoid dendritic-cell neoplasm. *N Engl J Med* 2019;380:1628–1637.
2. Stock W, Luger SW, Advani AS, et al. A pediatric regimen for older adolescents and young adults with acute lymphoblastic leukemia: results of CALGB 10403. *Blood* 2016;133:1548–1559.
3. Jain N, Roberts KG, Jabbour E, et al. Ph-like acute lymphoblastic leukemia: a high-risk subtype in adults. *Blood* 2017;129:572–581.