

# CLINICAL UPDATE

Current Developments in the Management of BPDCN

## Treatment Advances in Blastic Plasmacytoid Dendritic Cell Neoplasm



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### **H&O** What is blastic plasmacytoid dendritic cell neoplasm (BPDCN)?

**NP** BPDCN is an aggressive cancer of the blood and bone marrow that presents clinically as a hybrid of lymphoma and leukemia. In 2008, the World Health Organization (WHO) classified BPDCN under the heading “Acute myeloid leukemia (AML) and related precursor neoplasms.” In 2016, WHO reclassified BPDCN as a separate myeloid malignancy, reflecting a greater understanding of this unique disease. BPDCN manifests primarily as skin involvement, followed by bone marrow and finally lymph node involvement. Patients with BPDCN have traditionally had poor outcomes, and until recently no approved therapies were available. However, on December 21, 2018, the US Food and Drug Administration (FDA) approved tagraxofusp-erzs (Elzonris, Stemline Therapeutics), formerly called SL-401. This agent received priority review, breakthrough therapy designation, and orphan drug designation.

### **H&O** How common is BPDCN?

**NP** As with most rare diseases, including rare cancers, the true epidemiology is unknown. Complicating matters is the fact that rare diseases such as BPDCN tend to undergo numerous nomenclature changes—BPDCN has gone through a half dozen or more name changes over the past 30 years. Finally, when a disease is rare, it becomes difficult to nail down a diagnosis; dermatologists, pathologists, and primary care physicians may all encounter problems in identifying the illness in the first place.

The classification system of myeloid neoplasms and acute leukemia published by WHO in 2016 included

BPDCN, which should facilitate the diagnosis. The triad of CD123, CD4, and CD56 should be identified with immunohistochemistry and/or flow cytometry to diagnose this blood cancer. Other markers, such as TCL-1, CD303, and TCF4, are helpful in differentiating BPDCN from other closely related or mimicking conditions, such as AML with leukemia cutis. In addition, clinicians have become more aware of BPDCN than they formerly were now that an approved treatment is widely available.

I participated in a study published in *Leukemia Research* in 2018 in which we identified 219 patients with BPDCN in the Surveillance, Epidemiology, and End Results (SEER) database, which represents just a few regions in the United States. This figure is consistent with an incidence of 0.04 cases per 100,000. The typical survival of patients in this database was approximately 14 months, which is consistent with the survival noted in European studies and the historical literature.

### **H&O** How has BPDCN typically been treated?

**NP** Until recently, the treatment of BPDCN was not standardized. Groups worldwide borrowed their treatment approaches from those used in acute lymphoblastic leukemia (ALL), AML, or lymphoma. Our center, for example, has opted to administer therapy based on that used in ALL, which consists of multiagent chemotherapy (most commonly hyper-CVAD [cyclophosphamide, vincristine, doxorubicin, dexamethasone]) and central nervous system prophylaxis (usually with lumbar punctures), followed by stem cell transplant during first remission. The median age of patients with BPDCN is 70 years and older in most series; thus, because most elderly patients in the real world cannot receive full doses of multiagent

myelosuppressive chemotherapy, novel targeted therapies are needed that can be administered to patients of all ages, including older patients with BPDCN.

### H&O What is the prognosis for this disease?

**NP** Unfortunately, the historical prognosis has been dismal. Patients tend to respond to intensive combination chemotherapy at first, but they soon relapse and die of their disease. Most case series have reported a median overall survival ranging from 8 to 14 months. Overall survival numbers have improved, however, especially in those younger patients who are able to receive a stem cell transplant.

### H&O Could you talk more about tagraxofusp-erzs?

**NP** Tagraxofusp-erzs, which is the first agent to be approved specifically for use in BPDCN, has been approved for patients 2 years of age and older. It targets the interleukin 3 (IL-3) receptor alfa, also known as CD123, which is overexpressed in BPDCN. Although tagraxofusp-erzs was designed to be used in a number of different hematologic malignancies, early in vitro and in vivo studies showed potency against BPDCN specifically.

I had the opportunity to be involved in the phase 1/2 study of SL-401 published in *Blood* in 2014, with Dr Frankel as the first author. In this study, we treated 11 patients who had BPDCN with a single course of daily intravenous SL-401 at a dose of up to 12.5 µg/kg on days 1 through 5 of a 21-day cycle. Major responses to a single course of treatment occurred in 7 of 9 (78%) evaluable patients, including 5 complete responses and 2 partial responses. The median duration of response was 5 months, with a range of 1 to more than 20 months. The most common adverse events, which resolved after cessation of treatment, were fever, chills, hypotension, edema, hypoalbuminemia, thrombocytopenia, and transaminasemia.

On the basis of this encouraging experience, we were able to conduct the first large multicenter, multicycle trial of a targeted therapy specifically for patients with BPDCN; I most recently presented the results of this trial at the American Society of Hematology (ASH) annual meeting in December 2018. In this study, we built on the results of the earlier trial and enrolled additional patients with both untreated and relapsed/refractory BPDCN. The key objective was to further define safety (phase 1) and efficacy (phase 2). The inclusion criteria and exclusion criteria were important; in addition to the usual requirement for adequate organ function, we required a baseline albumin level of 3.0 g/dL at the beginning of the trial that was later amended to 3.2 g/dL in recognition of capillary leak syndrome.

### H&O How does tagraxofusp-erzs work?

**NP** Tagraxofusp-erzs, which is designed to target the IL-3 receptor, has a unique mechanism of action. The base of the drug is a truncated diphtheria payload in which one part of the diphtheria toxin is replaced with a human recombinant IL-3–fused protein. We believe that the cells that preferentially accept the drug when it is infused into the body are those that overexpress CD123 (IL-3 receptor alfa), which is the case in nearly all patients with BPDCN. We hypothesize that the drug is then internalized and causes irreversible protein synthesis, which is a targeted mechanism for killing cells.

### H&O What side effects are seen with tagraxofusp-erzs?

**NP** One of the most common side effects of tagraxofusp-erzs is transaminitis, which occurs in more than half of patients. This side effect is usually grade 1 or 2 and

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generally occurs in the first cycle of administration. Another common side effect is thrombocytopenia. All of these side effects occur primarily in the first cycle and do not appear to contribute to cumulative toxicity in nearly all cases. The most notable side effect, as observed in the 2014 study by Frankel and colleagues in *Blood*, was the occurrence of capillary leak syndrome. In light of this, the ongoing clinical trial has parameters for following the creatinine level in addition to monitoring liver function, patient weight, and fluid status. We also have recognized that capillary leak syndrome is more likely to develop in patients with a low albumin level, and so this is why albumin levels are monitored and replaced during the course of follow-up.

### H&O What other treatment approaches are being investigated?

**NP** We are also looking at targeting CD123 through different mechanisms. For example, researchers at several institutions are in the early stages of developing chimeric antigen receptor (CAR) T cells that target CD123. One

of these phase 1 studies is ABC123 (Study to Evaluate the Safety and Clinical Activity of UCART123 in Patients With BPDCN; NCT03203369), which is specifically studying patients with BPDCN. ABC123 is being conducted here at MD Anderson and at Weill Cornell Medicine in New York City. City of Hope in Duarte, California, also is recruiting patients for a study of the use of CD123-directed CAR T cells in BPDCN (NCT02159495).

Other efforts are aimed at targeting BCL-2, which has become an active area of research in both myeloid and lymphoid malignancies since the introduction of the small-molecule inhibitor known as venetoclax (Venclexta, AbbVie/Genentech). Venetoclax recently gained FDA approval for use in older patients with AML in combination with other agents. In addition, our group, in collaboration with Dana-Farber Cancer Institute in Boston, Massachusetts, recently reported in a paper published in *Cancer Discovery* that BCL-2 is overexpressed in BPDCN. On the basis of that study, our institutions have opened a phase 1 clinical trial of venetoclax in patients with BPDCN (NCT03485547).

### H&O What made you decide to focus on BPDCN in your career?

**NP** A passion for understanding an ultra-rare hematologic disease and cancer such as BPDCN has been a part of my life for at least the last 10 years. I treated several patients earlier in my career who died of BPDCN, and it was especially difficult to see them succumb to a disease whose name few people could pronounce and for which no active or approved targeted therapies were available. I began to ask the question, Is there anything more we can do for these patients? I had great support in particular from 2 people at MD Anderson—my chairman, Dr Hagop Kantarjian, and my mentor, Dr Marina Konopleva. Both of them urged me to take on this field as my career niche—not only to acquire a better understanding of BPDCN but also to see if new approaches and new ways to target the disease could be developed.

### H&O Is there anything that you would like to add?

**NP** Patients with ultra-rare diseases sometimes feel lost or alone, and I do not want anyone to feel that way. With the democratization of information in the era of the Internet and other digital resources, and with the molecular science becoming so sophisticated, we are now

able to divide diseases that were previously unknown or unknowable into smaller, more understandable subdiseases. By doing that, people like me and others on my team can subspecialize in these rare diseases. When you have a rare disease, it's not rare to you. It's what you and your loved ones are facing; the disease is not *rare*, it is a disease. I encourage people to understand that researchers are out there who are working on the rarest of the rare diseases. On Twitter, you can find out what is going on in the research community by using the #BPDCN hashtag.

### Disclosure

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### Suggested Readings

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