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Current Developments in the Management of Leukemia, Lymphoma, and Myeloma

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Blastic Plasmacytoid Dendritic Cell Neoplasm

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

NP BPDCN is a rare disease of the bone marrow and blood that affects multiple organs, including the lymph nodes and the skin. It often presents as leukemia or evolves into acute leukemia. The term refers to a malignant *neoplasm*, or cancer, that affects *blastic*, or immature, plasmacytoid dendritic cells. The World Health Organization standardized the term *blastic plasmacytoid dendritic cell neoplasm* in 2008, listing it under "acute myeloid leukemia and related neoplasms."[1] The name has been changed at least half a dozen times over the past several decades as our biological understanding of the disease has evolved, causing further confusion about this disease. Some of the most common previous terms in the literature are *blastic natural killer lymphoma* and *CD4+/CD56+ hematodermic tumor.*

H&O How rare is BPDCN?

NP We do not have a very good estimate of the incidence of BPDCN because it is so rare and also because historically it has been such a difficult disease to diagnose definitively. We know based on work by Pagano and colleagues that it likely accounts for fewer than 1% of all hematologic malignancies, and fewer than 1% of primary cutaneous lymphomas.[2]

H&O Who is affected by BPDCN?

NP Unlike most other leukemias, BPDCN has a pronounced male predominance; approximately 75% to 90% of cases occur in men. Although there are various reasons for this, the exact etiology is still being worked out. My colleague Dr Andrew Lane addressed this phenomenon in a compelling study presented at the 2013 American Society of Hematology (ASH) Annual Meeting.[3] The study described frequent, recurrent, somatic loss-of-function mutations in the splicing factor *ZRSR2* in patients with BPDCN. Of note, *ZRSR2* is located on chromosome Xp22.1. All 10 of the patients with BPDCN who had mutations in *ZRSR2* (frameshift, nonsense, or splice site mutations) were male. The researchers hypothesized that BPDCN might be more common in men owing to this observed gene dosage effect related to involvement of the X chromosome and the location of *ZRSR2*. BPDCN also tends to be a disease of older patients, with a median age at onset of anywhere from 60 to 70 years and older in some series. Of course, we do see this disease in female and pediatric patients as well. In general, however, as my colleagues and I noted in a poster at the 2015 ASH Annual Meeting, BPDCN tends to be a disease of older men.[4]

H&O What is the typical presentation of patients with this disease?

NP The vast majority of patients—70% or more—already have or acquire skin lesions. The lesions can be mild and small, or they can be pronounced and extensive, covering the entire body in some cases. In my experience, they often have a purplish discoloration. Regardless of the size, the lesion in question needs to be biopsied. Other patients have a more traditional leukemic presentation, which means low blood cell counts and the presence of blasts in the bone marrow, such as are seen in acute myeloid leukemia (AML) and acute lymphocytic leukemia (ALL). In the third type of presentation, patients have involvement of the lymph nodes, spleen, liver, or central nervous system, or they have extramedullary involvement—in which the disease occurs outside the bone marrow. In other words, this disease can present in essentially any location.

H&O How is BPDCN diagnosed?

NP The diagnosis of BPDCN has evolved over time as clinical and pathologic technologies have improved. As with most leukemias and lymphomas, the diagnosis was once based on morphology alone—the appearance of skin and bone marrow cells under the microscope. In addition to morphology, we now routinely use immunohistochemistry and flow cytometry to determine whether the cells are positive for the classic triad of BPDCN: CD4, CD56, and CD123. There is a fourth marker, T-cell leukemia/lymphoma 1 (TCL1), that our group and others have shown to be helpful in pinning down a diagnosis. Finally, we can use cytogenetics to aid in making a diagnosis. Chromosomal karyotype, flow cytometry, and molecular features can sometimes can help to differentiate this condition from other, similar diagnoses, such as AML, ALL, and cutaneous T-cell lymphoma.[5]

H&O What is the prognosis?

NP Outcomes historically have been quite poor for patients with BPDCN, which is one of the reasons I have made this rare disease the focus of my career. Even after it has been factored in that this disease tends to affect an older population, the outcomes in the largest series to date have been dismal. Most patients survive for only 10 to 14 months after diagnosis, despite receiving various chemotherapeutic regimens.[6]

Here at MD Anderson, we have observed a median overall survival of approximately 23 months, with the vast majority of these patients treated outside clinical trials with cytotoxic chemotherapy plus or minus stem cell transplant, per the updated abstract I presented with my colleagues at the most recent ASH Annual Meeting. Outcomes were poor regardless of the patient's age and regardless of a skin-only or a bone marrow presentation. Before the current era of targeted therapy, the patients with the best outcomes were those who were younger, had a complete remission, and received a stem cell transplant during first remission.[4]

Some newer studies that have come out over the past 5 or 6 years suggest that the use of allogeneic[6] or, interestingly, autologous[7] transplant can improve median survival to 2 to 4 years.

H&O How is BPDCN treated?

NP We have not had a uniform, consensus, worldwide standard of care treatment for BPDCN, so those of us who have been seeing patients with this disease have treated it as best as we can with available therapies. For example, some groups use chemotherapy regimens designed for AML or ALL. Another approach is to treat the disease like non-Hodgkin lymphoma, with cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP). The use of multiple-agent, intensive chemotherapy has the potential to produce remissions, but relapse tends to occur quickly. Patients die either of active disease in the setting of relapse or of infections or multiple-organ failure very quickly after relapse.

Because these outcomes are so dismal, and the majority of patients are older or have significant comorbidities precluding a stem cell transplant, there is an urgent need for novel, targeted therapies to improve the treatment of BPDCN.

H&O How well do we understand this condition?

NP As is the case in many rare cancers, we are in the early stages of understanding the disease. The fact that we pinned down the current name and a specific category of disease for BPDCN only 8 years ago is striking.[1] Although we still do not know very much about this disease, the fact that we can now use positivity for CD4, CD56, and CD123 has been a major improvement in diagnosis over the past 10 years. One thing that I am excited about is that CD123 appears to be overexpressed in essentially 100% of cases and is readily accessible for tumor targeting with the newer approaches.[8]

H&O What are some of the most important studies on BPDCN?

NP In 2014, Dr Art Frankel and coauthors, including me and Dr Marina Konopleva from MD Anderson, published the first-ever prospective trial of patients with BPDCN. This was a multicenter trial that enrolled 11 patients, of whom 9 were evaluable for response. What was remarkable about the trial was that essentially a single cycle of therapy with diphtheria toxin DT388-IL3, which is now known as SL-401 (Stemline Therapeutics), produced an objective response in 7 of the 9 patients. Of these, 5 patients had complete remissions and 2 had partial remissions, with a median duration of response of 5 months (range, 1-20+ months).[9]

Building on these results, we set out to do formal phase 1 and phase 2 clinical trials, testing with multiple cycles of SL-401. We undertook a study with 2 arms: one for patients with AML and the other for patients with BPDCN. In the updated results for the patients with BPDCN (presented as a poster at the 2015 ASH Annual Meeting), 12 of 14 evaluable patients with BPDCN (86%) had major objective responses, including 8 with complete responses (57%).[10] Based on these major responses in the phase 1 study, we are now moving to the planned stage 2 portion of the trial for patients with BPDCN.

This ongoing multicenter clinical trial has demonstrated thus far that it is safe and feasible to use multiple cycles of SL-401 in patients with BPDCN. Another important finding of the trial is that clinical benefit—such as a reduction in bone marrow blasts and skin lesions—

appears to occur in all subsets of patients, including those with skin-only disease, those with bone marrow involvement, and those with bulky disease.

One of the main side effects of SL-401 that occurred early on was capillary leak syndrome, which can result in fluid overload. Through regular monitoring, which includes measuring albumin levels, daily weight, and creatinine levels, we were able to identify this side effect quickly and address it in the early stages of the clinical trial. Since those measures were put into place, patients have been able to tolerate the drug overall quite well, as we discussed in our ASH abstract.[4]

H&O Are other studies looking at treatment for this condition?

NP So far, this trial of SL-401 is the only one specifically dedicated to BPDCN. Another trial I am aware of that includes patients with BPDCN, among other CD56-expressing tumors, is with the study drug lorvotuzumab mertansine, which targets CD56 in a variety of hematologic malignancies. This trial (An Open-label Phase II Study of Lorvotuzumab Mertansine) is currently open at our institution (NCT02420873).[11]

H&O What should be done to improve our understanding of and treatment options for this disease?

NP Monoclonal antibodies, chimeric antigen receptor (CAR) T-cell therapies, and a class of drugs called dual-targeting agents or bispecific molecules are in development; they have the ability to target CD123, CD56, and other antigens that may be applicable to patients with BPDCN. These novel targeted agents should be studied for use in BPDCN over the next 1 to 2 years and could represent the next exciting direction in therapeutic drug development and targeting.

In addition to developing ways to address the targets we know about, we need to look for additional targets in BPDCN. There have been some larger-scale efforts to start molecular sequencing in these patients to identify novel targets. For example, our group and several others have found that *TET2* mutations are common in patients with BPDCN. Large-scale exome/whole-genome sequencing efforts should and must continue to help unravel further the molecular complexity of BPDCN and identify novel targets for therapies.[5,12,13]

H&O Can you see a wider role for stem cell transplants?

NP Yes. So far, allogeneic stem cell transplant has been the most frequently used/reported modality in our field. A very interesting direction is that of autologous stem cell transplants. Aoki and colleagues published a paper in *Blood* last year that included 11 patients with BPDCN who underwent autologous stem cell transplant and had an overall survival rate of 82% at 4 years.[7] Given this positive data set for a small number of patients with autologous stem cell transplant, it would be of interest to see a focused study that directly compares autologous stem cell transplant vs allogeneic stem cell transplant for patients with BPDCN. We would like to know how the type and timing of transplant affect outcomes in this rare disease.

Disclosures

Research funding, advisory board, or consulting: Stemline, Novartis, Roche Diagnostics, LFB, Incyte, and Cellectis.

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