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RESEARCH ARTICLE

Efficacy and manageable safety of tagraxofusp in blastic plasmacytoid dendritic cell neoplasm: a case series of pediatric and adolescent/young adult patients

Naveen Pemmaraju[1] | Branko Cuglievan[1] | Joseph Lasky[2] | Albert Kheradpour[3] | Nobuko Hijiya[4] | Anthony S. Stein[5] | Soheil Meshinchi[6] | Craig A. Mullen[7] | Emanuele Angelucci[8] | Luciana Vinti[9] | Tariq I. Mughal[10,11] | Anna B. Pawlowska[12]

[1]Department of Leukemia, The University of Texas MD Anderson Cancer Center, Houston, Texas, USA

[2]Cure 4 The Kids Foundation, Las Vegas, Nevada, USA

[3]Department of Pediatric Hematology and Oncology, Loma Linda University Children's Hospital, Loma Linda, California, USA

[4]Division of Pediatric Oncology, Hematology, and Stem Cell Transplantation, Columbia University Irving Medical Center, New York, New York, USA

[5]Department of Hematology and Hematopoietic Cell Transplantation, City of Hope National Medical Center, Duarte, California, USA

[6]Department of Pediatrics, University of Washington School of Medicine, Seattle, Washington, USA

[7]Division of Pediatric Hematology/Oncology, Department of Pediatrics, Golisano Children's Hospital, University of Rochester, Rochester, New York, USA

[8]Hematology and Cellular Therapy Unit, IRCCS Ospedale Policlinico San Martino, Genova, Italy

[9]Department of Paediatric Haematology/Oncology, Cell and Gene Therapy, Bambino Gesù Children's Hospital, IRCCS, Rome, Italy

[10]Division of Hematology-Oncology, Tufts University Medical School, Boston, Massachusetts, USA

[11]Consultant to Stemline Therapeutics Inc, New York, New York, USA

[12]Department of Pediatrics, City of Hope National Medical Center, Duarte, California, USA

Correspondence
Anna B. Pawlowska, Department of Pediatrics, City of Hope National Medical Center, 1500 E. Duarte Road, Duarte, CA, 91010, USA.
Email: apawlows@coh.org

Abstract

Blastic plasmacytoid dendritic cell neoplasm (BPDCN) predominantly occurs in adults ≥60 years old; 10–20% of cases are pediatric or adolescent/young adult (AYA) patients. Tagraxofusp (TAG, Elzonris®) is the only approved treatment for BPDCN; in the United States it is approved for patients aged ≥2 years. Data on treating pediatric and AYA BPDCN patients are limited. We present a case series of pediatric and AYA patients with BPDCN treated with TAG. Eight patients (five newly diagnosed; three relapsed/refractory [R/R]), aged 2–21 years, received 12 mcg/kg TAG. Seven patients were female; most had skin (n = 6) and/or bone marrow (n = 4) involvement. No new safety signals were identified. Grade 3 adverse events were headache (n = 1) and transaminitis (n = 2). Three patients with newly diagnosed BPDCN achieved complete response, one achieved partial response, and one had stable disease (SD). One patient with R/R BPDCN achieved a minor response; one had SD. Seven patients (88%) were bridged to stem cell transplant: 80% of newly diagnosed patients and 100%

of R/R patients. Five patients remained alive at last follow-up. These cases highlight the efficacy and safety of TAG in pediatric and AYA patients for whom there is no other approved BPDCN therapy.

KEYWORDS
AYA BPDCN, CD123, pediatric BPDCN, plasmacytoid dendritic cells, tagraxofusp

1 | INTRODUCTION

Blastic plasmacytoid dendritic cell neoplasm (BPDCN) is an aggressive hematologic malignancy with a poor prognosis that is derived from the precursors of plasmacytoid dendritic cells [1, 2]. The incidence of BPDCN is roughly 500–1000 cases per year in the United States; global point prevalence is roughly 12/100,000. The incidence is higher for those ≥60 years old, with a median age range at diagnosis of 65–70 years [1–3]. Pediatric cases of BPDCN account for 10–20% of total cases [4–7] and anecdotal case reports suggest the clinical presentation is similar in adults and children.

Most patients present with skin and bone marrow (BM) involvement; a small proportion present with the disease in other extramedullary sites, in particular, lymph nodes (LN) and the central nervous system (CNS) [8–10]. A recent United States study indicated that BPDCN may have a bimodal age distribution with the first peak seen in children and adolescents [1].

Prior to approval of tagraxofusp (TAG, Elzonris®; the only United States Food and Drug Administration [FDA]-approved treatment for BPDCN in adults and children), standard induction acute lymphoblastic leukemia (ALL), acute myeloid leukemia (AML), or lymphoma-type chemotherapy regimens were the only available treatments [7, 9, 11–14]. However, the use of traditional chemotherapy is associated with high rates of toxicity, treatment-related death, and relapse [2, 12, 15–18]. Therefore, a strong need existed for novel therapies for the treatment of BPDCN.

TAG, a recombinant human interleukin-3 fused to a truncated diphtheria toxin payload, is a therapy directed toward CD123, which is overexpressed in BPDCN [19–22]. In 2018, the FDA approved TAG for use in patients ≥2 years with newly diagnosed or relapsed/refractory (R/R) BPDCN [23, 24]. TAG has also been approved by the European Medicines Agency for the treatment of newly diagnosed adult patients with BPDCN [25]. TAG approval was based on safety and efficacy data from a pivotal study with TAG monotherapy (NCT02113982). The overall response rate was 75%, with a complete response (CR) + clinical CR (CRc) of 57%, and a median duration of CR + CRc of 24.9 months. Of the patients achieving CR + CRc, 51% were bridged to stem cell transplant (SCT) [26]. Although no pediatric patients were enrolled in the pivotal study, the FDA approval of TAG for this population was based on the biological similarity of BPDCN in adults and children, and promising real-world data where pediatric patients treated with TAG showed rapid and significant clinical improvement and no adverse safety signals [27].

We present a case series of pediatric and adolescent/young adult (AYA) patients with BPDCN treated with TAG, to provide further insight into the efficacy and safety of TAG in this population.

2 | METHODS

This was a multicenter collation of case reports of pediatric and AYA patients (≤21 years old) diagnosed with BPDCN at six centers in the United States and Europe. All patients were treated according to local institutional guidelines and received TAG either as first-line treatment or for R/R disease. Data were collected retrospectively through chart review and summarized descriptively. Safety was assessed through monitoring of adverse events (AEs) and laboratory abnormalities. Efficacy was evaluated through tumor responses and survival.

2.1 | Patient demographics and clinical characteristics

Patient demographics, disease presentation, and individual case details are summarized in Tables 1 and 2. Clinical data were collected from eight pediatric/AYA patients; five (62.5%) patients received TAG as first-line therapy, and three (37.5%) as treatment for R/R disease. Clinical presentation at diagnosis included six patients with skin involvement, five with BM involvement, and three with LN involvement. For newly diagnosed BPDCN, all patients received 12 mcg/kg TAG daily for 5 days; one patient received 7 mcg/kg TAG at the second relapse.

2.2 | Case presentation

2.2.1 | Patient 1

A 16-year-old female patient presented with large bilateral posterior auricular, submandibular, right supraclavicular, and bilateral axillary lymphadenopathy. Additionally, she had ecchymotic lesions on her back, as well as yellow-brown and erythematous patches. Incisional biopsy of the left cervical node, BM biopsy, and skin lesion biopsy revealed BPDCN (plasmacytoid cells with CD123 positivity). Lumbar puncture showed CNS involvement. A positron emission tomography

TABLE 1 Patient characteristics and TAG treatment.

Characteristic	Patients $N = 8$
Median age, years (range)	15.5 (2–21)
Sex, *n* (%)	
Female	7 (87.5)
Male	1 (12.5)
Treatment, *n* (%)	
First-line	5 (62.5)
R/R	3 (37.5)
Presentation, *n* (%)	
Skin lesions	6 (75.0)
Bone marrow involvement	4 (50)
Lymph node involvement	3 (37.5)
TAG dose, *n* (%)	
12 mcg/kg	8 (100.0)
7 mcg/kg[a]	1 (12.5)
TAG cycles, median (range)	3.5 (1–4)

Abbreviations: R/R, relapsed/refractory; TAG, tagraxofusp.
[a]Patient 8 received TAG at 12 mcg/kg during treatment at the first relapse and at 7 mcg/kg at the second relapse.

(PET) scan was positive for diffuse LN enhancement and mildly increased BM activity.

The patient received four cycles of systemic TAG monotherapy at 12 mcg/kg daily on days 1–5 and five doses of intrathecal (IT) cytarabine, followed by triple IT chemotherapy (methotrexate, cytosine arabinoside, and hydrocortisone) for three doses. Subsequent evaluation revealed CNS negativity after four doses of IT chemotherapy. A BM biopsy after two cycles of TAG therapy was negative for disease and for minimal residual disease (MRD).

The patient was bridged to allogeneic (allo-)SCT. As of last follow-up (33 months since TAG initiation), the patient was alive with no history of graft-versus-host disease (GVHD).

TAG therapy was well tolerated with no AEs reported.

2.2.2 | Patient 2

A 20-year-old male patient presented with hyperpigmented annular skin lesions on his scalp, face, upper back, and extremities. Histology from skin biopsies of the lesions initially led to a diagnosis of leukemia cutis; however, after a subsequent review of the histology, the patient was diagnosed with BPDCN. A lumbar puncture and MRI were performed upon confirmation of diagnosis. There was no evidence of CNS involvement, and the BM was negative for disease. The patient received systemic TAG monotherapy at 12 mcg/kg daily on days 1–5. In cycle 1, only two doses were administered (days 1 and 2), with a CR to initial therapy. Cycle 2 was delayed (patient's request) and commenced 10 weeks after completion of cycle 1. At this point, the patient had recurrent skin lesions and bone pain consistent with leukemic dissemination and received a third cycle of TAG.

Following completion of cycle 3, no further benefit from TAG monotherapy was seen. The patient received combination therapy consisting of two cycles of 12 mcg/kg TAG on days 4–6, with azacitidine and venetoclax (21 days) as second-line therapy. After two cycles, the patient achieved a CR and was bridged to matched sibling donor SCT. The patient relapsed and died of sepsis 13 months after SCT.

On day 2 of cycle 1 of TAG monotherapy, the patient experienced grade 2 capillary leak syndrome (CLS), elevated aspartate aminotransferase (AST)/alanine aminotransferase (ALT), and hypoalbuminemia (albumin 3.2 g/dL). CLS was successfully managed by dose interruption and steroid treatment; it resolved within 4 days.

2.2.3 | Patient 3

A 16-year-old female patient presented with a single large 6-cm round lesion on the right leg. Skin biopsy revealed a diagnosis of BPDCN (plasmacytoid cells with CD123 positivity). PET and computed tomography (CT) imaging were negative. Flow cytometric analysis revealed no evidence of BM or CNS involvement.

The patient received four cycles of systemic TAG monotherapy at 12 mcg/kg on days 1–5 and achieved a partial response (PR).

A repeat skin biopsy 26 days following the last cycle showed minimal skin infiltration of CD123-positive cells. A single course of fludarabine, high-dose cytarabine, idarubicin, and granulocyte colony-stimulating factor (FLAG-IDA) + local radiotherapy was given, and the patient was bridged to haploidentical SCT. As of last follow-up (16 months since TAG initiation), the patient was alive and in CR, with 100% donor engraftment.

The patient experienced growth hormone deficiency while on, and immediately after, TAG treatment. No additional AEs were reported, and at last follow-up, the patient had no evidence of combined growth hormone deficiency.

2.2.4 | Patient 4

A 15-year-old female patient presented with thoracic pain and diffuse osteoarticular pain. CT imaging showed multiple pathologic abdominal and inguinal LNs. The patient had no cutaneous involvement but had BM involvement, with 70% blasts. Flow cytometry analysis of an inguinal LN biopsy was positive for CD4, CD33, CD45, CD56, CD123, HLA-DR, and CLL-1, confirming a diagnosis of BPDCN. Lumbar puncture showed no CNS involvement.

The patient received four cycles of TAG at 12 mcg/kg on days 1–5 every 3 weeks and achieved a morphologic CR after cycle 1, which was maintained until cycle 3. BM histology after cycle 3 showed 3–5% blasts. In cycle 1, TAG treatment was interrupted for CLS resolution after day 1, restarted at day 5, but was interrupted due

TABLE 2 Patient cases.

Patient no.	Age (years)/sex	Presentation	Disease compartment	Prior treatment	TAG treatment	Best response	Safety	Status at time of reporting	Survival from TAG initiation
1	16/F	Bilateral posterior auricular and submandibular adenopathy Right supraclavicular and bilateral axillary lymphadenopathy	BM, skin, and CNS	N/A	Four cycles (12 mcg/kg), days 1–5 (+ IT chemotherapy)	CR; bridged to SCT	No AEs reported	Alive post-SCT	33+ months
2	20/M	Raised skin lesions on the scalp and upper back	Skin	N/A	**1L**: Three cycles (12 mcg/kg), days 1–5 **2L**: Two cycles (12 mcg/kg), days 4–6 (TAG + AZA + VEN)	**1L**: SD **2L**: CR; bridged to SCT	Low albumin, transaminitis (AST 37, ALT 130), G2 CLS (treated, resolved after 4 days), G3 headache, and G3 transaminitis after C1D2	Died 13 months after SCT	~20 months
3	16/F	Large 6-cm lesion on the right leg	Skin	N/A	Four cycles (12 mcg/kg), days 1–5	Good PR with skin MRD (biopsy positive); bridged to allo-SCT[a]	Growth hormone deficiency	Alive post-haploidentical SCT	16 months
4	15/F	70% BM infiltration Abdominal and inguinal LN involvement	BM and lymph node	N/A	Four cycles (12 mcg/kg), days 1–5	Morphologic CR; histologic evaluation after C3 showed 3–5% blasts; bridged to MUD SCT	Rash (G1), CLS (G2), and transaminitis (G3) all during C1	CR (BM) following 1 cycle of FLAG-liposomal doxorubicin; disease-free post-MUD SCT	6+ months
5	21/F	Enlarging 3-cm lesion on left calf	Skin	N/A	Four cycles (12 mcg/kg), days 1–5	SD	Headache, hot flashes, fatigue, mouth sores	Died. Was recommended hyper-CVAD + VEN followed by SCT, but died prior to receiving SCT (PD)	11.5 months
6	10/F	Skin lesion on the left cheek	Skin, BM, and LN	Chemotherapy per AML protocol and SCT (relapsed)	Two cycles (12 mcg/kg), days 1–5, as part of induction prior to the second SCT	SD; bridged to SCT	No AEs reported	Second SCT complicated by mild GVHD that resolved; currently no evidence of disease (BM and PET-CT negative 1 year post-SCT)	12+ months

(Continues)

TABLE 2 (Continued)

Patient no.	Age (years)/sex	Presentation	Disease compartment	Prior treatment	TAG treatment	Best response	Safety	Status at time of reporting	Survival from TAG initiation
7	15/F	Skin lesion on the left breast	Skin	ADE induction; HDAC + etoposide intensification	One cycle (12 mcg/kg), days 1–5	PD; developed CNS disease; bridged to SCT	Grade 1 hypoalbuminemia	Hyper-CVAD + VEN and twice-weekly LP + IT; molecular remission achieved, followed by SCT	36+ months
8	2/F	Fever, otitis media, anemia, thrombocytopenia and neutropenia	BM	ALL-type chemotherapy regimen[b]; relapsed during maintenance. COG AALL07P1 reinduction block 1	**2L**: Two cycles (12 mcg/kg) days 1–5[c]; **3L**: One cycle (7 mcg/kg) days 1–3 (TAG + AZA + VEN)	**2L**: minor response[d]; bridged to SCT **3L**[e]: PD	**2L**: Transaminitis after C1 (AST 216, ALT 87), normalized in C2 **3L**: Transaminitis (AST 216, ALT 128)	Died. Was admitted to hospice, went into remission, and died more than 400 days later	~22 months

Abbreviations: 2L, second line; 3L, third line; ADE, daunorubicin and cytarabine with etoposide; AE, adverse event; ALL, acute lymphoblastic leukemia; ALT, alanine aminotransferase; AML, acute myeloid leukemia; Ara-C, cytarabine; AST, aspartate aminotransferase; AZA, azacitidine; BM, bone marrow; C, cycle; CLS, capillary leak syndrome; CNS, central nervous system; COG, Children's Oncology Group; CR, complete response; CT, computed tomography; D, day; F, female; FLAG, fludarabine, high-dose cytarabine, granulocyte colony-stimulating factor; G, grade; GVHD, graft-versus-host disease; hyper-CVAD, cyclophosphamide, vincristine, doxorubicin, and dexamethasone; HDAC, high-dose Ara-C; IT, intrathecal; LN, lymph node; LP, lumbar puncture; M, male; MRD, minimal residual disease; MUD, matched unrelated donor; N/A, not available; PD, progressive disease; PET, positron emission tomography; PR, partial response; SCT, stem cell transplant; SD, stable disease; TAG, tagraxofusp; VEN, venetoclax.

[a] Following a single course of FLAG-IDA + local radiotherapy on the residual lesion.

[b] On the basis of COG AALL1131.

[c] Patient required albumin infusions prior to TAG.

[d] On the basis of BM morphology and flow.

[e] Patient relapsed at 7 months post-SCT.

to another CLS event; treatment resumed at day 9. Cycle 1 was completed on day 10 with no further events. A BM biopsy following cycle 4 showed 10–15% blasts, and treatment with FLAG-liposomal doxorubicin (Myocet®) chemotherapy was initiated for relapse. As of last follow-up, the patient is alive, post-SCT, having achieved a CR following one cycle of FLAG-liposomal doxorubicin; survival is >6 months after TAG initiation.

The patient experienced grade 1 rash and grade 3 transaminitis; both occurred in cycle 1 and were resolved. The patient also experienced grade 2 CLS events in the first cycle on days 1 and 6 (following TAG restart after the previous interruption). CLS was treated with TAG interruption and administration of albumin, furosemide, and dopamine in both instances.

2.2.5 | Patient 5

A 21-year-old female patient initially presented with an enlarging 3-cm skin lesion on the left calf. BPDCN was diagnosed from a skin punch biopsy. A BM biopsy performed concurrently showed no evidence of BM involvement by flow cytometry and there was no evidence of CNS involvement. PET imaging showed no other signs of active disease.

The patient received four cycles of TAG therapy at 12 mcg/kg daily on days 1–5 every 3 weeks, resulting in stable disease (SD) and persistent skin disease in the original lesion. The next planned treatment was cyclophosphamide, vincristine, doxorubicin, and dexamethasone (hyper-CVAD) + venetoclax, followed by SCT; however, the patient died before receiving further treatment. Survival was 11.5 months after initiation of TAG.

The patient experienced headache, hot flashes, fatigue, and mouth sores while on TAG, with each event managed successfully. There were no reports of CLS or transaminitis.

2.2.6 | Patient 6

A 10-year-old female patient presented with a bluish, nodular skin lesion on the left cheek. She had a lesional punch biopsy and was diagnosed with BPDCN. The patient also had BM involvement and a left periauricular node/lesion.

She received two cycles of daunorubicin and cytarabine with etoposide (ADE) induction chemotherapy, followed by intensification cycle 1, at which point she underwent an allo-SCT. At 90 days post-transplant, BM aspirates and biopsies showed no evidence of BPDCN disease or GVHD. At 1-year follow-up, a BM biopsy revealed 10–15% positive BM BPDCN disease. Subsequent PET-CT imaging showed widespread nodal disease and a large pelvic mass. Induction chemotherapy was restarted and after two cycles, the mass had disappeared. PET-CT scans showed an excellent overall response and BM aspirate showed no, or only residual, disease. The patient then received high-dose methotrexate per an interim maintenance Children's Oncology Group (COG) AALL1131 protocol without issue, followed by two cycles of 12 mcg/kg TAG daily on days 1–5, resulting in SD. The patient was bridged to a second SCT (haploidentical) and experienced mild GVHD, which resolved. The patient is currently alive 1-year post-SCT with negative BM and PET-CT scans; survival since initiation of TAG therapy is >12 months.

TAG was well tolerated; no AEs or abnormal laboratory parameters were reported.

2.2.7 | Patient 7

A 15-year-old female patient presented with a left breast skin lesion, which was initially misdiagnosed as myeloid sarcoma without BM or CNS involvement. The patient was treated with the COG AAML0531 pediatric protocol consisting of ADE induction chemotherapy (Ara-C [cytarabine], daunorubicin, and etoposide), followed by high-dose Ara-C + etoposide intensification. She achieved remission but experienced an isolated skin lesion relapse at the same location. At the time of relapse, a lesional skin biopsy was positive for CD123, CD4, TCL1A, HLA-DR, and CD33 (although negative for CD56) and the patient was diagnosed with BPDCN.

The patient received one cycle of TAG at 12 mcg/kg daily on days 1–5 but experienced progression and developed CNS disease. The patient discontinued TAG and hyper-CVAD + venetoclax therapy was initiated along with twice-weekly IT chemotherapy. The patient achieved molecular remission with negative MRD and received a successful SCT. As of last follow-up, the patient is alive post-SCT; survival is >36 months since the initiation of TAG therapy.

TAG was well tolerated; grade 1 hypoalbuminemia was reported, which improved following appropriate fluid adjustment.

2.2.8 | Patient 8

A 2-year-old female patient presented with a 1-week history of a febrile illness, and had otitis media, anemia, thrombocytopenia, and neutropenia. There was no lymphadenopathy, splenomegaly, hepatomegaly, or rash. BPDCN was diagnosed following a BM examination.

The patient was treated with ALL-type chemotherapy per the COG AALL1131 protocol but experienced relapse while receiving maintenance chemotherapy. Subsequently, she received ALL-type reinduction chemotherapy per the COG AALL07P1 reinduction block 1 protocol (doxorubicin, vincristine, prednisone, and pegylated asparaginase). As part of pretransplant therapy, the patient received two cycles of TAG 12 mcg/kg daily on days 1–5. Albumin levels prior to TAG were 2.8 g/dL, and the patient required albumin infusions before therapy could be initiated. Prior to TAG treatment, the BM contained 2% malignant cells, defined on the basis of marrow morphology and flow cytometry. The patient had a minor response after treatment. Before initiation of cycle 2, BM was morphologically normal. After cycle 2, flow cytometry showed <1% of the abnormal cells observed at diagnosis, and fluorescence in situ hybridization results for previously known translocations showed 6.5% abnormal cells. The patient was bridged to SCT, and a month later achieved a CR and negative MRD status.

However, she experienced relapse at 7 months posttransplant. Third-line therapy consisted of one TAG cycle at a lower dose of 7 mcg/kg daily on days 1–3 in combination with azacitidine (75 mg/m^2 per dose for seven doses) and venetoclax (150 mg daily for 21 days). No albumin infusions prior to therapy were required. After third-line therapy, the disease progressed and the patient was moved to hospice care 4 weeks after the last dose. The patient went into spontaneous remission with no sign of malignancy or evidence of disease in blood and BM assessments. After >400 days, the patient relapsed, received one dose of TAG (178 mcg) as salvage, but died soon afterward.

The patient developed transaminitis when TAG was given in the pre-transplant setting—it occurred after cycle 1 and normalized in cycle 2—and also after receiving TAG as a third-line therapy.

TABLE 3 Best response to TAG.

Outcomes	1L BPDCN $n = 5$	R/R BPDCN $n = 3$	All patients $N = 8$
Response to TAG, *n* (%)			
CR	3 (60)	0	3 (38)
PR	1 (20)	0	1
MR	0	1 (33)	1 (13)
SD	1 (20)	1 (33)	2 (25)
PD	0	1 (33)	1 (13)
Bridged to SCT, *n* (%)	4 (80)	3 (100)	7 (88)

Abbreviations: 1L, first-line; BPDCN, blastic plasmacytoid dendritic cell neoplasm; CR, complete response; MR, minor response; PD, progressive disease; PR, partial response; R/R, relapsed/refractory; SCT, stem cell transplant; SD, stable disease; TAG, tagraxofusp.

3 | DISCUSSION

BPDCN, a disease usually associated with older patients, also affects children and AYAs. TAG, the only approved treatment for BPDCN, is indicated for the treatment of patients ≥2 years old by the FDA, although there is limited information in the literature regarding its use in pediatric patients and AYAs. The first published experience using TAG to treat pediatric patients was in 2018, by way of three case presentations [27]. All patients received a 5-day infusion of TAG 12 mcg/kg/day every 2–3 weeks via compassionate use. TAG was well tolerated without significant toxicities. Two of the three cases had significant and rapid clinical improvement after two courses of treatment, although the response was transient; the third patient, who had R/R disease, had no response. The three cases supported the approval of TAG in patients ≥2 years old.

Through the cases discussed herein, we sought to gain a greater understanding of the optimal management of BPDCN in younger patients. The eight patient cases presented supplement the evidence base on the safety and efficacy of TAG therapy in pediatric and AYA patients. TAG had a manageable safety profile, with a similar AE profile to that seen in the adult population [26] and no unexpected safety signals. Two patients had no AEs. Two patients experienced grade 2 CLS events in cycle 1 that were successfully managed with dose interruption and either steroid or albumin, furosemide, and dopamine treatment. Both patients with CLS also experienced grade 3 transaminitis. While TAG was associated with elevation of AST/ALT, hypoalbuminemia, rash, headache, hot flashes, fatigue, and mouth sores, all AEs were managed successfully.

TAG showed promising antitumor efficacy. Of the five patients with newly diagnosed BPDCN, three patients achieved CR, and one achieved PR. One R/R patient achieved a minor response. Two patients achieved SD (one newly diagnosed; one R/R), and one R/R patient had progressive disease (Table 3). Seven patients (88%) were bridged to SCT with TAG or with combination therapy (TAG and chemotherapy): 80% of first-line patients and 100% of R/R patients.

One patient received TAG in combination with azacitidine and venetoclax. This patient had a CR and was bridged to SCT. Although a small sample size, these results imply that TAG can be combined safely with other agents. Additional studies are needed to confirm this, and the combination of TAG with azacitidine and venetoclax is currently being tested in a phase 1 clinical trial of adult patients with AML or BPDCN (NCT03113643) [28].

We note that in adults BPDCN has a strong male predominance, with a 3.5:1 male-to-female incidence [2, 6, 29]. In this series, seven of the eight patients (88%) are female. Other publications, including a 2017 literature review of 74 pediatric patients found that 33 of 74 (45%) patients were female [9], and a review of 69 BPDCN cases in patients aged ≤21 years found the cases were evenly split between genders [30]. While the clinical presentation of BPDCN is similar between pediatric/AYA and adult patients, reported observations indicate that the biology of cancers may differ by age [31]. Deleterious mutations affecting the DNA methylation pathway, such as *TET2*, have been found in nearly all adult BPDCN tumors [32], but in children, no driver mutations have been found to date. In addition, rearrangements in the proto-oncogene *MYB* appear to be more prevalent in children (100% in five cases) compared with adults with BPDCN (44% in nine cases) [33].

In our case series, most patients were AYAs, with only one pediatric patient. This is consistent with the age distribution reported in a review of 69 cases of BPDCN in patients aged ≤21 years for whom the mean age was 10 and most patients were older than 5.[30] In contrast, ALL has a reported peak incidence between 1–4 years of age [34] underscoring BPDCN's unique biology.

4 | CONCLUSION

This multicenter, retrospective case series of eight pediatric and AYA patients with BPDCN increases the available information on BPDCN treatment in younger individuals. Overall, better responses were achieved when TAG was administered earlier in treatment. In conclusion, TAG was efficacious with a manageable safety profile in all patients, and, importantly, seven (88%) out of eight patients reported herein were bridged to SCT.

AUTHOR CONTRIBUTIONS

All authors were involved in the concept and development of the manuscript. Naveen Pemmaraju, Branko Cuglievan, Joseph Lasky, Albert Kheradpour, Craig A. Mullen, Emanuele Angelucci, and Luciana Vinti provided the patient cases. All authors reviewed and approved the final manuscript.

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The data that support the findings of this study are available from the corresponding author upon reasonable request. The data are not publicly available due to privacy or ethical restrictions.

ETHICS STATEMENT

All procedures in this study were performed in accordance with the principles of the Declaration of Helsinki and the institutional guidelines.

PATIENT CONSENT STATEMENT

The patients, their legal representatives, or their next of kin provided written informed consent for the publication of the data and any related information.

CLINICAL TRIAL REGISTRATION

The authors have confirmed clinical trial registration is not needed for this submission.

ORCID

Naveen Pemmaraju https://orcid.org/0000-0002-1670-6513

Anna B. Pawlowska https://orcid.org/0000-0001-9466-6396

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