Critical Reviews in Oncology/Hematology 107 (2016) 156–162

Contents lists available at ScienceDirect

Critical Reviews in Oncology/Hematology

journal homepage: www.elsevier.com/locate/critrevonc

A critical review of treatment modalities for blastic plasmacytoid dendritic cell neoplasm

Umberto Falcone, Hassan Sibai, Uday Deotare (M.D., D.M.)*

Department of Medical Oncology and Hematology, Princess Margaret Cancer Centre, University Health Network, Toronto, Canada

Contents

ARTICLE INFO

Article history:
Received 1 June 2016
Received in revised form 12 August 2016
Accepted 20 September 2016

Keywords:
Blastic plasmacytoid dendritic cell neoplasm
HyperCVAD
Allogeneic hematopoeitic cell transplant
Autologous hematopoeitic cell transplant

ABSTRACT

Blastic plasmacytoid dendritic cell neoplasm (BPDCN) is a clinically aggressive tumor derived from the precursors of plasmacytoid dendritic cells. It is a rare disease presenting across all ages with either skin or both skin and bone marrow involvement often conferring a poor prognosis. Though localized radiation has been used before, acute leukemia based regimens, remains the treatment of choice for induction of remission. Hematopoietic stem cell transplant, either autologous or allogeneic, is further required for attaining sustained remissions. Recently, a number of targeted therapies and newer drugs have been used as the molecular and genetic understanding of the disease have improved.

1. Introduction to a rare but common disease

Blastic plasmacytoid dendritic cell neoplasm (BPDCN) is a clinically aggressive tumor derived from the precursors of plasmacytoid dendritic cells (pDCs) (Petrella and Facchetti, 2010). Although it is often diagnosed on skin biopsies because of the high frequency of primary cutaneous involvement, progression of disease and

* Corresponding author at: Department of Medical Oncology and Hematology, Princess Margaret Cancer Centre, 610, University Avenue, Toronto, Ontario, M5G 2M9, Canada.
E-mail address: Uday.Deotare@uhn.ca (U. Deotare).

http://dx.doi.org/10.1016/j.critrevonc.2016.09.003
1040-8428/

leukemic dissemination appear to be part of the natural evolution of BPDCN (Petrella and Facchetti, 2010). The striking cutaneous tropism of BPDCN cells has been attributed to their expression of antigens, such as CLA and CD56, that favor skin migration, and to the local availability of chemokines receptors expressed by neoplastic plasmacytoid dendritic cells (CXCR3, CXCR4, CCR6, CCR7) (Lanier et al., 1991).

BPDCN is a rare disease, representing only 0.76% of cases presenting in the leukemic phase as acute leukemia (Bueno et al., 2004). In World Health Organization (WHO), BPDCN is classified within acute myeloid leukemias (AML) and related precursor neoplasm (Facchetti et al., 2008). Menezes et al. (2014) performed whole-exome sequencing of 3 BPDCN cases and their data support the current WHO classification of the disease as a myeloid disorder. However, debate still exists about the disease origin with both Acute Lymphoblastic Leukemia (ALL) and AML based regimens used for treatment and achieving success in obtaining variable periods of remissions (Bueno et al., 2004). The rarity of this disease makes it to be easily misdiagnosed, and there is a significant delay between the onset of lesions and the final diagnosis (Julia et al., 2013). BPDCN has no ethnic predilection; it is more frequent in the elderly with a median age of 67 years, but it can occur at any age. Though exceedingly rare in paediatric population, it has been reported in as young as 8 months old child (Nguyen et al., 2015). There is a gender predominance with a male/female ratio of 3.3:1 (Feuillard et al., 2002; Herling and Jones, 2007; Jacob et al., 2003).

The diagnosis of BPDCN is based on immunophenotypic criteria, either by Flow cytometry or immunohistochemistry. In addition to CD4, CD56, HLA-DR and CD123 positivity, other pDC associated antigens such as TCL1, BDCA-2 and CLA are positive. Other lineage specific antigens, needs to be negative (Lin-) (Facchetti et al., 2008). The differential diagnosis of BPDCN usually are cutaneous infiltrating hematological malignancies such as NK/T cell leukemia/lymphoma, cutaneous T cell lymphoma and myelomonocytic acute leukemias. Immunophenotypic analysis are positive for CD4 (bright), CD33 (dim), CD56 (heterogenous), CD123 (bright), CD36, CD38, HLA DR and CD71 (Deotare et al., 2016).

Although the clinical presentation of BPDCN may be at times indolent, the disease invariably progresses and prognosis remains poor, with a median overall survival (OS) ranging from 9 to 20 months (Julia et al., 2013; Feuillard et al., 2002; Herling and Jones, 2007; Jacob et al., 2003; Pagano et al., 2013; Dalle et al., 2010; Petrella et al., 2005; Rauh et al., 2012). Patients with skin involvement at diagnosis have been reported to have a better prognosis(Lucioni et al., 2011), however no prognostic factors have been clearly identified at the present time. Clinical presentation, genetic (Lucioni et al., 2011) and molecular (Marafioti et al., 2008) characteristics as well as chemokine expression (Hashikawa et al., 2012) have been postulated as possible prognostic factors, capable of identifying more aggressive forms of BPDCN, but there is no clear evidence till date. Terminal deoxynucleotidyl transferase (TdT) negative with BDCA-2 positive phenotype seems to confer a worse prognosis in some studies (Jaye et al., 2006; Angelot-Delettre et al., 2015). Recently, monoallelic deletion of NR3C1 (which encodes the glucocorticoid receptor) leading to haploinsufficiency and glucocorticoid resistance was associated with extremely poor prognosis (Emadali et al., 2016).

The rarity of this disease explains absence of extensive literature regarding its management. In a recent review of the English literature from 1966 to 2012, only 240 publications relevant to BPDCN were identified (Kharfan-Dabaja et al., 2013). To date, there is no standard treatment for BPDCN and data from randomized clinical trials are lacking. This review is focused on appraising the available treatment modalities and to help make evidence based therapeutic decisions.

2. Treatment modalities in BPDCN

2.1. Disease localized to the skin

BPDCN can present with localized lesions to the skin. It invariably progresses to become systemic, with bone marrow and peripheral blood involvement. Systemic steroids and low-dose chemotherapy represent valuable options for localized disease. Local radiotherapy (LRT) has been used in patients with isolated skin lesions, especially those who are not deemed to be candidate to chemotherapy because of comorbidities or advanced age, and those with recurrent disease after systemic chemotherapy.

A few cases of primary cutaneous solitary BPDCN with single skin localization at diagnosis have been reported and treatment varies from RT to aggressive approaches with leukemia-type chemotherapy regimens (Sugimoto et al., 2013). Chemotherapy regimens derived from the treatment of limited-stage NK/T-cell lymphomas have also been tried for patients with BPDCN, with complete remission (CR) sustained for more than one year, anecdotally in an elderly patient treated with a simultaneous combination of dexamethasone, VP16, Ifosfamide, carboplatin (DeVIC) chemotherapy and L-asparginase (Sugimoto et al., 2013).

Ishibashi et al. (2015), reviewed the literature concerning patients receiving initial treatment with radiation therapy, alone or in combination with chemotherapy (various regimens), for BPDCN-related skin lesions. Of the 23 patients reported, 14 (60.9%) received RT alone as initial treatment. Although the study is limited by the fact that RT dose was not reported for most of the treated patients, 13/14 achieved a response (CR = 8/14, 57%) while only 1/14 showed progressive disease (PD). The therapeutic efficacy of LRT and its optimal dose remains unclear. Despite these encouraging responses to radiation treatment, the disease usually recurs in a few months, progressing to systemic disease and bearing a poor prognosis (Dalle et al., 2010; Ishibashi et al., 2015). Hence, BPDCN localized to the skin should be treated with systemic cytotoxic regimens instead of localized therapy.

2.2. Systemic disease

There is no established standard first-line therapy for advanced-stage BPDCN patients and randomized controlled clinical trials are lacking. Participation in clinical trials, though few, should be encouraged across treatment centers all throughout the world considering the rarity of this disease. Patients with BPDCN are more commonly treated with chemotherapy regimens derived from the therapeutic management of other more common hematological malignancies such as non-Hodgkin lymphoma (NHL), ALL and AML.

2.2.1. CHOP-like chemotherapy regimens

In 2002, Reimer and colleagues (Reimer et al., 2003) reviewed 91 published cases of BPDCN and evaluated clinic-pathological aspects including type of treatment and outcome. The initial response rate to treatment was high with CR and partial remission (PR) rates of almost 70% and 10%, respectively. Only about 20% of patients showed a sustained remission (median observation: 16 months) while the majority experienced relapse and eventually died of disease. CHOP-like regimens yielded overall response rates (ORR) of about 70% (55% CR) in 38 evaluable patients (Reimer et al., 2003).

In the same period, Feuillard et al. (2002) reported CR rates of 86% in 23 patients treated with different chemotherapy regimens. Nine patients had received CHOP-like chemotherapy and CR rate was approximately 78% in 7/9 patients (Reimer et al., 2003).

2.2.2. Acute leukemia-type chemotherapy regimens

Published literature shows that most patients with BPDCN have been treated with leukemia based regimens (Table 1). These reg-