On behalf of the National Cancer Research Institute Haematology Clinical Studies Groups

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L-asparaginase with methotrexate and dexamethasone is an effective treatment combination in blastic plasmacytoid dendritic cell neoplasm

Blastic plasmacytoid dendritic cell neoplasm (BPDCN) is a rare disease characterized by an aggressive clinical behaviour and a remarkably poor prognosis. It predominantly affects elderly males with an average age of 67 years at diagnosis and the affected organs are usually the skin, bone marrow, lymph nodes and central nervous system (Dalle *et al*, 2010). Most patients often respond to acute leukaemia–like chemotherapy, but relapses are almost inevitable, with median overall survival (OS) of 8–12 months in the largest patient series (Dalle *et al*, 2010; Pagano *et al*, 2013). Although BPDCN was classified as a myeloid malignancy in the 2008 World Health Organization classification, one recent retrospective study suggested that patients receiving an acute lymphoid leukaemia (ALL)/lymphoma-type regimen had a better response and better survival (Pagano *et al*, 2013). The importance of allogenic haematopoetic stem cell transplantation (allo-HSCT) to sustain remission was emphasized in both this and other trials (Pagano *et al*, 2013; Roos-Weil *et al*, 2013). Given that there is no consensus on the optimal therapeutic approach in this rare and aggressive disease, we chose to combine L-asparaginase with methotrexate, two synergistic drugs used in ALL treatment, insensitive to the multidrug resistance pathway and able to prevent central nervous system involvement.

Blastic plasmacytoid dendritic cell neoplasm was diagnosed in seven patients and confirmed by histopathology and flow cytometry using the criteria proposed by Garnache-Ottou *et al* (2009). These patients were treated in our institution with the AspaMetDex (L-asparaginase, methotrexate, dexamethasone) regimen between March 2006 and November 2012. All patients received three 21-d cycles of the (AspaMetDex) protocol, consisting of intravenous L-asparaginase (Kidrolase; EUSA Pharma, Oxford, UK) 6000 units/m^2 of body surface area on days 2, 4, 6, and 8, plus methotrexate 3 g/m^2 on day 1, and oral dexamethasone 40 mg from days 1–4. AspaMetDex regimen was continued until allo-HSCT or progression for responding patients. Patients who had allergic reactions to the L-asparaginase injections subsequently received Erwinia asparaginase (20 000 u/m^2, Erwiniase; EUSA Pharma) with the same schedule. Antithrombin and fibrinogen serum levels were measured before each injection of L-asparaginase. Patients with serum antithrombin levels below 60% of normal or fibrinogen levels under 0·5 g/l were given replacement therapy. All patients received alkaline hydration and leucovorin rescue with methotrexate, and anti-infectious prophylaxis with trimethoprim-sulfamethoxazole and valacyclovir. The primary endpoint was the response rate after three cycles assessed by clinical examination, bone marrow aspiration with flow cytometry and skin biopsy. Secondary endpoints were relapse-free survival (RFS), OS, and toxicity (Serious adverse events were graded according to the National Cancer Institute Common Toxicity Criteria, Version 3, http://ctep.cancer.gov/protocolDevelopment electronic_applications/docs/ctcaev3.pdf).

The clinical and laboratory characteristics of patients are described in Table I. We analysed six males and one female, with a median age at diagnosis of 59 years (range, 54–73). All of them had skin and medullary involvement at diagnosis. One patient had been previously treated with six courses of CHOP (cyclophosphamide, doxorubicin, vincris-

Table I. Patient characteristics.

Patient	Age, years	Sex	ECOG PS	Initial staging	Garnache-Ottou score	Cytogenetics	Previous treatment	Response to first line therapy
1	59	M	0	S+, N+, Blood−, BM+	2	Normal	No	NA
2	56	M	1	S+, N−, Blood+, BM+	2	No metaphases	No	NA
3	54	M	1	S+, N+, Blood−, BM+	2	Iso (×21)	No	NA
4	73	M	1	S+, N+, Blood−, BM+	2	Unknown	NHL-type	CR (12 months)
5	65	F	0	S+, N−, Blood+, BM+	2	Normal	AML-type	NR
6	70	M	1	S+, N+, Blood+, BM+	2	Normal	No	NA
7	59	M	1	S+, N+, Blood+, BM+	2	Normal	No	NA

ECOG PS, Eastern Cooperative Oncology Group performance score; M, male; F, female; S, skin; N, lymphadenopathy; BM, bone marrow; NA, not applicable; CR, complete remission; NR, no response; NHL, non-Hodgkin lymphoma; AML, acute myeloid leukaemia.

tine, prednisolone) that induced a complete remission (CR) with a RFS of 12 months. Another patient was refractory to an acute myeloid leukaemia (AML)-type induction. The AspaMetDex regimen was given as front line therapy in the other five cases.

Table II summarizes the treatment outcomes. The median number of cycles was six (range, 1–8). After three cycles of treatment, 5/7 patients had responded (71%) with 4/7 having CR (57%). The best response was obtained after three courses for all of them. Three of the five patients who had responded after three cycles relapsed, 2, 9 and 10 months (median, 9 months) after the end of treatment. Two of four patients who achieved a CR proceeded to allo-HSCT. Both of them were still alive in CR at the time of analysis, with a follow-up of 14 and 47 months. The median survival was 12·1 months (range, 2–47) and the median RFS was 10 months (range, 2–47). The main adverse events (grade 3–4) were three infections (one *Pseudomonas aeruginosa* septicaemia, one *Candida tropicalis* fungaemia and one *Pneumocystis jirovecii* pneumopathy), one acute renal failure, one pulmonary embolism, one left ventricular dysfunction and one case of gastritis. The antithrombin level fell to <60% of normal in four patients and they thus received antithrombin infusions (Aclotine®; LFB, Les Ulis, France). No diabetes or pancreatitis occurred. One refractory patient died of fungal infection associated with haemophagocytic lymphohistiocytosis after one cycle of treatment.

The best treatment for these patients remains a matter of debate and there are currently no recommendations in this setting. BPDCN are considered as the malignant counterpart of normal plasmocytoid dentritic cells (PDC; Chaperot *et al*, 2001). The lineage assignment of PDC and BPDCN to either a myelomonocytic or lymphoid derivation is still unclear. The hypothesis of a myeloid origin is reinforced by the fact that myelodysplasia or AML are seen during the course of BPDCN and that *TET2* mutations can occur with similar features to those in other myeloid neoplasms (Jardin *et al*, 2009). However, studies on genomic and transcriptomic profiles are less in favour of this myeloid origin (Dijkman *et al*, 2007). Some studies have already demonstrated the superiority of ALL-compared to AML-type regimens (Tsagarakis *et al*, 2010). Recently, Pagano *et al* (2013) pointed out the superiority of an ALL-type regimen in terms of both response and OS. In this study, patients treated with an AML-type regimen had an OS of 7·1 months *versus* 12·3 months for those receiving an ALL-type regimen ($P = 0{\cdot}02$) (Pagano *et al*, 2013). We found a similar survival of 12·1 months in our study with the AspaMetDex regimen. This alternative therapy has already been reported in small series to have the same high efficacy (Fontaine *et al*, 2009; Gilis *et al*, 2012). These three 'lymphoid' drugs might be an attractive approach for the treatment of BPDCN, while having the advantage of being well tolerated and feasible for the majority of patients who are too old or unfit to receive

Table II. Treatment and outcome.

Patient	Cycles (*n*)	Response after three cycles	Relapse	Relapse-free survival (months)	Allo-HSCT	Overall survival (months)	Outcome
1	8	CR	Yes	10	No	12	Died
2	4	NR	NA	NA	No	6	Died
3	7	CR	No	47	Yes	47	Alive in CR
4	4	CR	Yes	9	No	34	Died
5	1	NA	NA	NA	No	2	Died
6	6	PR	Yes	2	No	8	Died
7	6	CR	No	14	Yes	14	Alive in CR

Allo-HSCT, allogeneic haematopoietic stem cell transplantation; CR, complete response; PR, partial response; NA, not applicable.

an intensive therapeutic approach. Future prospective studies are warranted, before definitively supporting this strategy.

Author contributions

JPM designed the protocol and co-ordinated the study. BG and IV analysed the data and wrote the paper. JPM and BR critically reviewed the final version of the paper. All the other authors participated in the data collection, analysis and interpretation.

Conflict of interest

The authors report no potential conflict of interest.

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Absolute monocyte count at diagnosis and survival in mantle cell lymphoma

We read with great interest the recent article regarding the prognostic impact of monocyte count at presentation in mantle cell lymphoma (von Hohenstaufen *et al*, 2013). In this article, the absolute monocyte count (AMC) at diagnosis was identified as an independent predictor for survival when compared with the Mantle Cell Lymphoma International