Leukemia Research 42 (2016) 43–46

Contents lists available at ScienceDirect

Leukemia Research

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

Comparison of vindesine and prednisone and cyclophosphamide, etoposide, vindesine, and prednisone as first-line treatment for adult Langerhans cell histiocytosis: A single-center retrospective study

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ARTICLE INFO

Article history:
Received 26 July 2015
Received in revised form
29 December 2015
Accepted 24 January 2016
Available online 28 January 2016

Keywords:
Histiocytosis
Langerhans-cell histiocytosis
Adult
Multisystem
Chemotherapy

ABSTRACT

Objective: We compared the efficacy and clinical outcomes of vindesine and prednisone (VP) and cyclophosphamide, etoposide, vindesine, and prednisone (CEVP) regimens as first-line treatment for multisystem (MS) or multifocal single system (SS-m) adult Langerhans cell histiocytosis (LCH).
Method: Clinical features, treatment response, and survival of adults with Langerhans cell histiocytosis treated at our center from January 2001 to January 2015 were reviewed retrospectively.
Results: Forty-five adult MS or SS-m LCH patients were treated ($N = 31$, CEVP group; $N = 14$, VP group). Both treatment groups had similar gender distributions, patient ages, and extent of disease. The non-active disease rate for both groups was 70.0% and 64.3% ($P = 0.775$), respectively. Median follow-up was 74.9 (range: 2.8–183.6) months and recurrence rates were 71.0% and 78.6% ($P = 0.593$), respectively. The need for second-line therapy was 64.5% and 71.4% ($P = 0.649$), respectively, and mortality rates were 9.7% and 15.4% ($P = 0.586$), respectively. Neutropenia occurred in 48.4% of CEVP-treated patients and 7.1% of VP-treated patients ($P = 0.008$).
Conclusions: CEVP or VP regimens for the treatment of adult SS-m or MS LCH showed similar efficacies, and both regimens were associated with high disease recurrence and the need for second-line therapy.

1. Introduction

Treatment for multisystem Langerhans cell histiocytosis (MS LCH) is well established in children but poorly defined in adults. Combination chemotherapy for pediatric multifocal single system (SS-m) and MS LCH patients usually consists of etoposide or vinblastine [1,2]. The DAL-HX study described the non-randomized use of prednisone, etoposide, vinblastine, 6-mercaptopurine, and methotrexate for 12 months in pediatric patients [1], which resulted in a 23% recurrence rate, suggesting that more prolonged and intensive therapy may substantially improve long-term outcomes. In contrast, randomized trials conducted by the Histiocyte Society involving pediatric patients confirmed that treatment with vinblastine or etoposide was associated with similar responses, toxicity, and survival, but disease recurrence was as high as 56%, suggesting that pediatric MS LCH is best managed with a combination therapy for one year [3]. A recent LCH-III trial indicated that extending therapy to 12 months decreases disease recurrence in low-risk (RO-MS) patients [4]; however, most of these studies involved pediatric patients.

The appropriateness and optimal use of these regimens in adult patients with LCH is unclear, and clinical trial using the VP regimen in adult MS LCH patients is currently being conducted at the international level because only a few eligible subjects were enrolled at the local setting. A recent long-term follow-up study showed that recurrence rates (36.8 versus 62.5%, respectively) and death rates (10.7 versus 24.0%, respectively) were lower in pediatric patients compared to that in adults [5]. In contrast to studies involving pediatric patients, adults are more likely to develop irreversible neurotoxicity after prolonged vinblastine treatment [6] and of secondary malignancies after long-term etoposide treatment [7]. Cladribine, as a single and combination drug with alkylating cytostatic drugs and corticosteroids, is effective and results in

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http://dx.doi.org/10.1016/j.leukres.2016.01.012
0145-2126/

Table 1
Patient characteristics, treatment outcomes, and adverse effects.

Characteristic	Total	CEVP	VP	*P* value
	N = 45	*N* = 31	*N* = 14	
Gender				
Female, *N* (%)	13 (28.9%)	11 (35.5%)	2 (14.3%)	0.146
Age (yrs), median (range)	31 (18–69)	30 (18–69)	34 (18–56)	0.455
Multisystem, *N* (%)	41 (91.1%)	29 (93.5%)	12 (85.7%)	0.393
Risk organ, *N* (%)	25 (55.6%)	18 (58.1%)	7 (50.0%)	0.614
Involved organ				
BM, *N* (%)	1 (2.2%)	1 (3.2%)	0 (0)	1.000
Liver, *N* (%)	7 (15.6%)	6 (19.4%)	1 (7.1%)	0.295
Spleen, *N* (%)	4 (8.9%)	2 (6.5%)	2 (14.3%)	0.393
Lungs, *N* (%)	22 (48.9%)	15 (48.4%)	7 (50.0%)	0.920
Courses of treatment (median, range)	5.5 (2 12)	5.5 (3 9)	5 (2 12)	0.848
PC (overall), *N* (%)	32 (71.1%)	21 (67.7%)	11 (78.6%)	0.724
Before treatment, *N* (%)	25 (55.6%)	16 (51.6%)	9 (64.3%)	0.525
After treatment, *N* (%)	7 (15.6%)	5 (16.1%)	2 (14.3%)	1.000
Response				
NAD, *N* (%)	31 (68.8%)	22(70.0%)	9 (64.3%)	0.875
AD, *N* (%)	9 (20.0%)	6 (19.4%)	3 (21.4%)	
PD, *N* (%)	5 (11.1%)	3 (9.7%)	2 (14.3%)	
Reactivation, *N* (%)	33 (73.3%)	22 (71.0%)	11 (78.6%)	0.593
Second-line therapy, *N* (%)	30 (66.7%)	20 (64.5%)	10 (71.4%)	0.649
Death, *N* (%)	5 (11.4%)	3 (9.7%)	2 (15.4%)	0.586
Adverse events				
Neutropenia, *N* (%)	16 (35.6%)	15 (48.4%)	1 (7.1%)	0.008
Thrombocytopenia, *N* (%)	4 (8.9%)	4 (12.9%)	0	0.294
Hepatic, *N* (%)	8 (17.8%)	7 (22.6%)	1 (7.1%)	0.402

Abbreviations: BM, bone marrow; yrs, years; PC, permanent consequences.

low toxicity in adult patients with MS LCH or aggressive multifocal LCH [8,9]. However, the cost of these regimens has limited its widespread use. In addition, the extended use of cladribine is associated with an increased risk for secondary malignancies [10]. Therefore, we retrospectively analyzed the efficacy and toxicity of cyclophosphamide, etoposide, vindesine, and prednisone (CEVP) and vindesine and prednisone (VP) in 45 untreated adults with SS-m and MS LCH at our medical center.

2. Materials and methods

2.1. Patients

Forty-five adults with newly diagnosed SS-m and MS LCH were evaluated at the Peking Union Medical College Hospital, China from January 2001 to January 2015. Thirty-one patients were treated with CEVP and 14 with VP. A retrospective review of patient records and continuous follow-up were performed. LCH was established based on histologic biopsy, immunohistochemistry, and accessory studies. The Ethical Institutional Review Board of the Peking Union Medical College Hospital approved the study.

2.2. Baseline and follow-up evaluation

Patients were uniformly screened for treatment and a history and physical examination was conducted, as well as a complete blood count with differential and platelet count, biochemistry panel, erythrocyte sedimentation rate, thyroid function test, bone marrow aspiration and biopsy, X-ray bone survey, high-resolution computed chest tomography, and an ultrasound scan of the abdomen and biopsy of the affected tissue or organs when feasible. Patients underwent a comprehensive evaluation as earlier described prior to each chemotherapy course. Patients were clinically assessed for treatment response four weeks after completion of three courses of chemotherapy. Patients were similarly staged at three-month intervals within the first year after response and at six-month intervals during the second year of the study.

2.3. Diagnostic criteria

Initial LCH patient evaluation included histopathologic evaluation of diagnoses and determination of disease extent. Histopathologic diagnosis was confirmed for all patients using S-100 and/or CD1a antigen positivity screening [11]. Extent of disease was confirmed with physical examinations, and laboratory and radiographic studies. Patients with MS were classified as high- (RO+) or low-risk (RO−) according to the extent of organ involvement. Hepatomegaly, liver function testing, or liver biopsy was employed to determine hepatic involvement. Splenic involvement was diagnosed by enlargement that exceeded 2 cm below the costal margin according to ultrasonography or radiographic evaluation. Involvement of the hematopoietic system and lungs were diagnosed as previously reported [12]. Single-system multifocal bone lesions were defined as lesions involving 2 or more unique bones.

2.4. Treatment

All patients received systemic chemotherapy at the discretion of the treating physician. Most patients received CEVP every 3 weeks, which consisted of cyclophosphamide (750 mg/m^2 IV on day 1), vindesine (4 mg, IV on day 1), etoposide (100 mg/m^2, IV on days 1–3), and prednisone (100 mg, PO on days 1–5). A few patients received VP, which consisted of vindesine (4 mg, IV once weekly) and prednisone (100 mg, PO on days 1–5 every 3 weeks).

2.5. Response and toxicity criteria

Treatment response was evaluated 4 weeks post-chemotherapy. Responses were classified as non-active (NAD), active (AD), or progressive disease (PD). NAD was defined as complete resolution or continuous regression of disease. AD was defined as either stable disease or a mixed response (a regression of disease but appearance of new lesions in another site or organ system). PD was defined as disease progression with no observable response. Patients with single-system multifocal bone lesions and regression or lesional stability after treatment were classified as NAD. Patients with new lesions or old lesions that enlarged were classified as PD [13].

Permanent consequences (PC) were defined as any form of permanent or irreversible physical or neuropsychological handicap attributable to the disease itself that developed at any time during the disease course. Clinical neurological or psychological deficits not associated with imaging findings were classified as neurological PCs. Neurodegenerative CNS lesions were defined as characteristic changes on brain MRIs with or without associated clinical signs and symptoms, and with or without confirmation by biopsy.

The National Cancer Institute Common Toxicity Criteria (CTCAE) was used to evaluate toxicity. Grade 3 or 4 toxicity was considered to be significant. Chemotherapeutic initiation was delayed until the absolute granulocyte count was >1.0 × 10^9/L and the platelet count was >100 × 10^9/L.

2.6. Statistical analysis

Cases were characterized using biochemical counts and proportions for categorical variables and means and ranges for continuous variables. Treatment responses for both groups were compared using the chi-square test and Fisher's exact test. *P* values <0.05 were considered statistically significant. The probability of survival or