



High-dose chemotherapy followed by autologous hematopoietic stem cell transplantation for adult histiocytic disorders with central nervous system involvement

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We postulated that high-dose chemotherapy (HDC) followed by peripheral autologous hematopoietic stem cell transplantation might help to control refractory central nervous system (CNS) histiocytic disorders. Six patients with histiocytic CNS involvement were treated in this way. Two patients achieved non-active disease status, although one relapsed at 84 months. Two patients had regressive disease, one of whom progressed at 21 months. One patient had progressive disease at 14 months. One patient had extra-CNS progression but CNS regression. After a median follow-up of 22.4 months, only one of the six patients still has non-active disease. Treatment was effective on craniofacial and space-occupying brainstem lesions, and was ineffective on neurodegenerative lesions.

Key words: histiocytic disorders, Erdheim-Chester disease, high-dose chemotherapy, refractory CNS involvement, autologous peripheral blood hematopoietic stem cell transplantation

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Histiocytic disorders are due to non-malignant proliferation of antigen-processing phagocytic cells or antigen-presenting cells. They cause a broad spectrum of clinical and histological manifestations and are difficult to treat. Histiocytic disorders are divided, for clinical reasons, into those arising from dendritic cells (e.g. Langherans' cell histiocytosis [LCH]) and those arising from interstitial dendrocytic cells (non-LCH histiocytic disorders such as Erdheim-Chester disease [ECD]).¹ Despite differences in their clinical manifestations, the adult forms of LCH and ECD are closely related and have been treated with the same drugs.²

Hypothalamic-pituitary involvement is frequent in LCH and ECD, whereas the rest of the central nervous system (CNS) is generally spared. All or part of the CNS may be involved; patients with such involvement usually also have extensive multisystemic disease or multiple bone lesions.^{2,3} CNS involvement in LCH has been extensively studied, because of the higher frequency of LCH in children. It can consist either of space-occupying histiocytic infiltrates leading to size- and site-dependent symptoms, or of progressive neurological deterioration with mainly cerebellar-pontine symptoms.⁴ CNS involvement is rarely present at diagnosis, progresses independently of extra-CNS

sites of involvement,⁵ and is frequently fatal despite various treatment approaches.

The optimal treatment strategies for CNS involvement in LCH and ECD have not yet been defined. Therapies known to be effective in systemic disease, and especially drugs such as etoposide (VP-16) that cross the blood-brain barrier,⁶⁻⁹ might be beneficial in this setting. High-dose chemotherapy (HDC) can also increase drug delivery to the CNS.¹⁰ Following our encouraging initial experience,¹¹ we postulated that intensive chemotherapy including high-dose etoposide, followed by autologous peripheral blood hematopoietic stem cell rescue, might help to control refractory histiocytic disorders with CNS involvement.

Design and Methods

We reviewed the files of all patients treated between 1997 and 2005 with HDC followed by autologous hematopoietic stem-cell transplantation for histiocytic disorders with CNS involvement refractory to several lines of therapy.

Diagnostic criteria

All diagnoses were confirmed by histological and immunohistochemical studies. LCH was defined as infiltration by histiocytes

Table 1. Patient characteristics and outcome after HDC with autologous hematopoietic stem cell transplantation (AH SCT).

	Patients' #1	Patient #2	Patient #3	Patient #4	Patient #5	Patient #6
Histology	ECD	LCH	LCH	ECD	ECD	LCH
Situation pre-HDC/AHSCT						
Age	23 years	45 years	35 years	44 years	39 years	36 years
Time from CNS onset	7.4 years	4.3 years	0.4 years	3.7 years	0.8 years	5.7 years
CNS lesions ¹	Type 1 Orbits, cranio-facial, skull base bones (sinuses)	Types 3, ND Cerebellum, brainstem, supra-tentorial lesions	Type 1, 3 Pia mater, frontal hemisphere	Type 1, 3, ND Facial and skull base, cerebellum, pons, atrophy	Type 1, 3 Corpus callosum, posterior cerebral fossa, orbits	Type 3 Cerebellum, brainstem
Extra-CNS lesions	Bone, left kidney	Lung, bone	Parietal bone	Limb bones, skin, maxilla, pleura, lung, aorta, mitral valve	Lung, aorta, coronary artery, skin, maxilla, retroperitoneum	Skin, lung, parotid
Previous treatments	IFN α , VBL, Cy, VCR, ST, VP16, 2CDA	VP16, MTX, ST, ATRA, VBL, 2CDA	Surgery x 2, ST, VBL	Anti-TNF α , IFN α , ST	VBL, MTX, ST, 6-MP, IFN α	VBL, IFN α , ST, 2CDA
Response after HDC/AHSCT						
CNS lesion responding	Type 1	Type 3	Types 1 and 3	ND	Type 1	Type 3
Initial Response	RD at 1 months	RD at 4 months	NAD at 3 months	PD	CNS RD at 2 months, but mediastinal/retroperitoneal PD	RD at 4 months
Maximal response	NAD at 14 months	RD at 16 months	NAD at 3 months	PD	PD	RD
LCH III classification ²	Better	Better	Better	Worse	Worse	Better
Relapse	Orbital at 84 months	Cerebellum, pons at 20.6 months	No	—	—	No
Overall Survival	97 months Alive with PD	31 months Dead of lung infection with PD	57 months Alive in NAD	14 months Alive with PD	8 months Alive with PD	7.4 months Alive with continuous RD

¹Classification of CNS involvement according to Prayer et al.²⁰ Type 1: craniofacial bone and skull base lesions with or without soft-tissue extension. Type 2: intracranial, extra-axial changes (hypothalamic-pituitary region, meninges, circumventricular organs). Type 3: intracranial, intra-axial changes (white matter and gray matter). Neurodegenerative (ND) changes were defined as hyperintensities on T1-weighted images in the cerebellar dentate nucleus, with hypo- or hyperintensity on T2-weighted images and possible extension to the perinuclear white matter, and/or T1-weighted images of the basal ganglia. Type 4: cerebral atrophy.²The response was evaluated with the scoring system of the Histiocytic Society Protocol LCH III.¹² The disease was considered as non-active (NAD) when resolution of all signs and symptoms was obtained. The disease was considered as active (AD) in all other cases (RD=regressing disease; SD = stable disease, persistence of signs and symptoms; PD= progressive disease, progression and/or appearance of new lesions). The response was considered as Better (NAD and RD), intermediate (new lesion in one site, regression in another site, or SD) or worse (PD). IFN α : interferon alpha, VBL: vinblastine, Cy: cyclophosphamide, VCR: vincristine, ST: steroid therapy, VP16: etoposide, 2CDA: 2-chloro-2'-deoxyadenosine, MTX: methotrexate, ATRA: all-trans-retinoic acid, TNF α : tumor necrosis factor alpha, 6-MP: 6-mercaptopurine.

expressing CD1a, CD68 and PS100, and ECD was defined as infiltration by foamy histiocytes negative for CD1a and PS100 and positive for CD68. Magnetic resonance imaging (MRI) was used to diagnose and classify CNS lesions according to the criteria for CNS LCH proposed by Prayer et al. (Table 1).

Characteristics of the patients and previous treatments

All the patients were men, with a median age of 36 years (range 23.8-45.9 y) at the time of HDC. They all had a long history of histiocytic disorders (6.5-15.8 years, median 7.6 years after initial symptom onset) and CNS involvement (0.4-7.4 years, median 4 years). All but one

(#3) of the patients had multisystem disease. The disorders were refractory to three to seven lines of therapy (median five), including surgery, steroids, chemotherapy, immunotherapy and experimental therapies. Disease status at the time of HDC is described in Table 1. All the patients received oral information on the HDC and autologous stem cell transplant procedure, in accordance with the Helsinki Declaration of 1975, revised in 2000.

Hematopoietic stem cell collection, conditioning and autologous stem cell transplant

Peripheral blood stem cells were harvested by leukapheresis after steady-state granulocyte colony-stimulating factor mobilization (G-CSF 10 μ g/kg/day). Apart

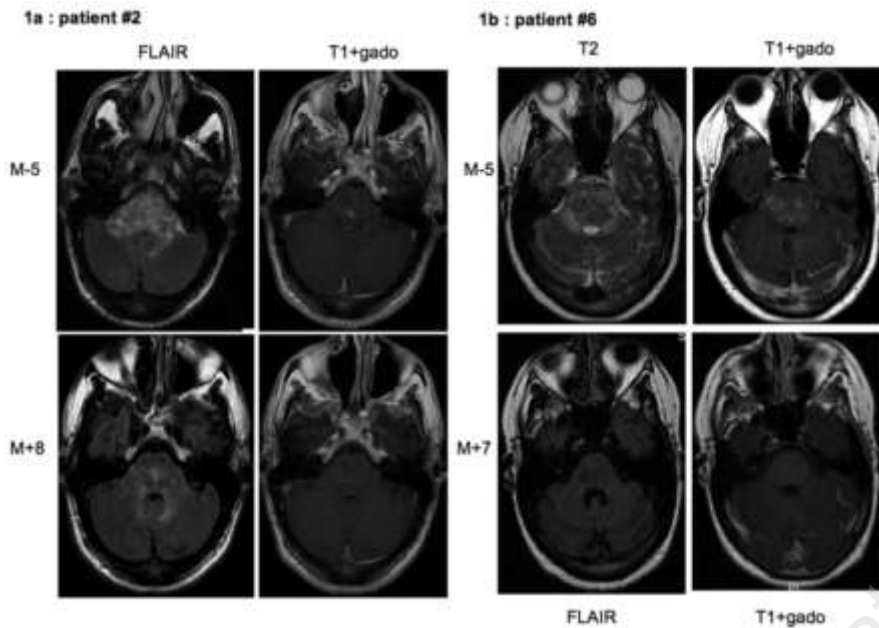


Figure 1. A. Patient #2 brainstem MRI lesions. Before (top) high-dose chemotherapy, axial T2-flair weighted image (left) showing a space-occupying lesion of the pons with patchy gadolinium enhancement on the axial spin echo T1-weighted image (right). Eight months after HDC (lower), the lesion on a T2-flair weighted image (left) has markedly shrunk, and contrast enhancement on the axial spin echo T1-weighted gadolinium enhanced image (right) is much reduced. **b.** Patient #6 brainstem MRI lesions. Before (top) high-dose chemotherapy, this axial spin echo T2-weighted image (left) demonstrates a space-occupying lesion of the brainstem with mass effect and patchy post-contrast enhancement on an axial spin echo T1-weighted image (right). Seven months after HDC (lower), the lesion on a T2-flair weighted image (left) has shrunk markedly, and post-contrast enhancement on an axial spin echo T1-weighted gadolinium image (right) is much reduced.

from patient #1, who has been described in detail elsewhere,¹¹ the patients received one course of intensive therapy, with carmustine (BCNU) 300 mg/m² on day-4, etoposide 60 mg/kg on day-3, and melphalan 140 mg/m² on day-1, followed by autologous hematopoietic stem cell rescue.

Definition of responses

Cerebral MRI scans were independently reviewed by a neurologist and two neuroradiologists. The responses were evaluated using the scoring system of the Histiocytic Society Protocol Langerhans' Cell Histiocytosis III, as described in Table 1.¹²

Results and Discussion

Feasibility

Autologous peripheral blood stem cells were successfully collected after G-CSF mobilisation in every case. A median of 6.9×10^6 CD34⁺ cells/kg (range 3.31 - 13.13×10^6 CD34⁺ cells/kg) were harvested, with a median of 38.19×10^4 /kg CFU-GM (range 18.58-92.47).

Tolerability of the conditioning regimen

No procedure-related deaths occurred. Engraftment was obtained in every case. Grade 3 infectious complications (n=5) consisted of *Staphylococcus epidermidis* central venous catheter infection in three cases, and were of unknown origin in two cases.

Efficacy and outcome of autologous hematopoietic stem cell transplantation

One patient (#4) had persistent continuous progressive brainstem neurodegenerative lesions 14 months after HDC, while the other CNS lesions and pulmonary dis-

ease were stable. Initial CNS responses were seen in the other five patients and concerned only space-occupying lesions of type 1 (n=3) or brainstem and intracerebral lesions of type 3 (n=2). Two patients entered complete remission, with non-active disease. The first patient (#1) had gradually regressive orbital disease from 1 to 14 months until non-active disease, followed by a local recurrence at 84 months. Eight years after HDC the patient was alive with persistent active disease. The second patient (#3) had non-active disease from 3 to 57 months after HDC (date of last follow-up) with no recurrence of a frontal CNS lesion and disappearance of bone contrast uptake on MRI. Two patients had regressive disease. The first patient (#2) had gradually regressive space-occupying brainstem disease from 4 to 16 months after HDC, with reduced contrast uptake and attenuation of the mass effect (MRI) (Figure 1A), together with a clinical improvement. His neurological status worsened 20.6 months after HDC (as confirmed by MRI), and he died 31 months after HDC of recurrent pulmonary infections due to swallowing disorders. The second patient (#6) was alive with gradually regressive CNS disease from 2 to 7.4 months (date of last follow-up), with regression of the space-occupying brainstem lesions and disappearance of contrast enhancement on MRI (Figure 1B), as well as the posterior pituitary hypersignal; this patient's clinical status also improved. Extra-CNS disease was stable. Thus, the initial responses were better in four cases (non-active disease in two cases and regressive disease in two other cases) and worse in two cases (one progressive disease and one discordant response). After a median follow-up of 22.4 months, only one of the six patients still had non-active disease.

This retrospective study describes the outcome of HDC after treatment with etoposide and peripheral autologous hematopoietic stem cell rescue in adults with

Table 2. Summary of published data on hematopoietic stem cell transplantation in LCH and ECD.

	Allogeneic HSCT Published cases Steinert's Series ¹⁹	Allogeneic HSCT Published cases ^{13,21,22}	Autologous HSCT Published cases ¹³⁻¹⁵	Our series
Conditioning regimen	Reduced, non-myeloablative	Myeloablative	Myeloablative	BCNU-VP16-Melphalan
HSCT type n	Allogeneic 9	Allogeneic 32	Autologous 5	Autologous 6
Death toxic disease	2 2 0	16 (50%) 14 2	3 1 2	1 0 1 (patient #2)
Alive AD	7 0	16 1	2 0	5 4
NAD duration (months)	7 8.4-29.4; (Median 13)	15 12-204* (Median 27)	2 84 and 96	1 57
Population	Childhood LCH-MS	Childhood LCH-MS ² Except one adult 29 years TBI/Cy/BCNU MSD died of relapse at 11.6 months no GVHD	Childhood LCH-MS Except one adult 45 years TBI/Cy ABMT Alive with NAD at 96 months	Adulthood LCH-MS LCH (n=3) ECD (n=3) CNS involvement

HSCT: hematopoietic stem cell transplantation; AD: active disease; NAD: non active disease, LCH-MS Langerhans' histiocytosis with multisystem disease; TBI: total body irradiation; CY: cyclophosphamide; MSD: matched sibling donor; GVHD: graft versus host disease; ABMT: autologous bone marrow transplantation; LCH: Langerhans cell histiocytosis; ECD: Erdheim Chester disease; CNS: central nervous system. *data non available for two patients.

histiocytic disorders complicated by refractory extra-pituitary CNS involvement. Although little information on the utility of intensive therapy in patients with histiocytic disorders is available, especially for adults (Table 3),¹³⁻¹⁵ we postulated that HDC might be beneficial. A multidrug HDC regimen rather than a conditioning regimen with total body irradiation was chosen, to avoid excessive toxicity.¹⁶ We opted for the etoposide-melphalan-carmustine combination, as these drugs have been widely used in HDC regimens;¹⁷ they are known to cross the blood-brain barrier and to be effective on cerebral sites of various malignancies. As it is important for the agents used in HDC regimens to have proven activity on the disease in question,¹⁷ we included etoposide, a drug used in severe multisystem LCH, both at diagnosis and in recurrent/refractory disease.⁶⁻⁹ Etoposide may also be effective in ECD.¹⁸

Five patients with multisystem LCH have previously received intensive therapy and undergone autologous stem cell transplantation; three died of LCH within 6 months with no disease control, while two were alive with non-active disease at 84 and 96 months.^{13,14} Allogeneic transplantation appears to have a graft-versus-LCH effect in childhood,^{13,19} but no relevant data are available for adult LCH or ECD. Apart from the patients

in the present series, only two adults with LCH have received high-dose chemotherapy with stem cell rescue (Table 2). In all but one of our six patients, both the CNS and the extra-CNS sites responded. CNS efficacy was maximal and most durable on craniofacial lesions, but partial efficacy was also obtained on some brainstem lesions. Only space-occupying brainstem lesions, which are generally considered as histiocytic granulomas,⁴ responded to HDC. No efficacy was observed on neurodegenerative lesions, which are described as neuronal and axonal degeneration associated with demyelination.⁴ CNS responses sometimes continued for several months (median 15 months) before disease stabilization or non-active disease. Lengthy remissions have been observed, in keeping with previous reports on HDC/ followed by autologous stem cell transplantation (median 5.9 years).¹³⁻¹⁵ Nevertheless, lengthy remissions can occur in the natural history of these diseases, possibly related to some mechanism of immune response, and connected with the pathogenesis of the disease, and these disease-free periods must be interpreted with care. Unfortunately, with a median follow-up of 22.4 months (7.4-97.3 months), only one patient in our series remains disease-free. In addition to the type (space-occupying or neurodegenerative lesions) and the location (craniofacial or intracranial) of CNS lesions, the tumor burden and previous treatments might have influenced the response rate and the response duration. Indeed, the patient with persistent, non-active disease had a short history of isolated skull and intracranial space-occupying LCH CNS lesions and a low tumor burden (the brain mass had been surgically removed before HDC), and had only received two lines of systemic treatment.

In conclusion, we suggest that space-occupying CNS lesions might be amenable to cure if HDC is performed in the disease course. Regular MRI could be useful to detect CNS lesions early in adult LCH and ECD with CNS alterations or symptoms. Better collaboration between internal medicine and hematology units might enable HDC and autologous hematopoietic stem cell transplantation to be performed in patients with refractory histiocytic CNS involvement.

NG: acquisition of data, analysis and interpretation of data, composition of the article; PB: acquisition of data, analysis and interpretation of data, composition of the cases report; JH: revising the paper critically for important intellectual content; BW: revising the paper critically for important intellectual content; EVDN: revising the paper critically for important intellectual content; KH-X: revising the paper critically for important intellectual content, interpretation of MRI; ZA: revising the paper critically for important intellectual content; RG: revising the paper critically for important intellectual content, interpretation of MRI; JS: revising the paper critically for important intellectual content, interpretation of MRI; NA: revising the paper critically for important intellectual content; J-CP: revising the paper critically for important intellectual content; VL: substantial contributions to conception and design, and analysis and interpretation of data. We thank Alain Fur for the follow-up of patient #1, and David Young for editing the manuscript.

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