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Up-Front Therapy for LCH: Is It Time to Test an Alternative to Vinblastine/Prednisone?

Stephen J. Simko, MD¹, Kenneth L. McClain, MD, PhD¹, and Carl E. Allen, MD, PhD¹

¹Baylor College of Medicine and Texas Children's Cancer Center, Houston, TX, USA

Keywords

Langerhans cell histiocytosis; LCH; vinblastine; prednisone; cytarabine

Langerhans cell histiocytosis (LCH) is an inflammatory myeloid neoplasia (Berres, *et al* 2014) occurring most commonly in children that can be fatal if “risk” organs (liver, spleen, bone marrow) are involved. Long-term consequences including endocrinopathies, sclerosing cholangitis and debilitating neurodegeneration remain problematic (McClain, *et al* 2011). Vinblastine plus prednisone is standard of care for children with *de novo* multisystem disease and has been the primary backbone utilized in 30 years of multinational trials (Gadner, *et al* 2013). While overall survival has steadily improved, outcomes for patients with LCH remain suboptimal. Approximately half of patients will fail to be cured with this approach, requiring extended or alternate therapy. The estimated five-year mortality in patients with risk organ disease remains approximately 15%, and the highest risks of death or disease complications are in patients who fail initial therapy (Gadner, *et al* 2013). Toxicities of vinblastine and prednisone include excessive weight gain, growth retardation and peripheral neuropathy. In our view, these outcomes with vinblastine/prednisone leave room for improvement.

Cytarabine has been administered as therapy for *de novo* LCH but has never been evaluated prospectively. Cytarabine was first utilized for multiorgan LCH in a regimen also containing vincristine and prednisone. Clinical remission occurred in 13/18 (72%) patients, including 5/8 patients with risk organ involvement (Egeler, *et al* 1993). In a retrospective series of adults treated for LCH, cytarabine monotherapy provided superior one-year disease-free survival with less toxicity than vinblastine/prednisone (Cantu, *et al* 2012).

We have reviewed the medical records of patients treated with cytarabine for both *de novo* and recurrent LCH at our institution from 2005–2013 (Table I). Thirty-eight patients were treated with cytarabine-containing regimens at 100–170 mg/m²/dose daily over 3–5 days

Corresponding authors: Stephen Simko, MD, 1102 Bates Avenue, Suite 750.01, Houston, TX 77030, USA, sjsimko@txch.org, Telephone: +1 (832) 824-4848, Fax: +1 (832) 825-1206, Carl Allen, MD, PhD, 1102 Bates Avenue, Suite 750.01, Houston, TX 77030, USA, ceallen@txch.org, Telephone: +1 (832) 824-4312, Fax: +1 (832) 825-1206.

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every 3–4 weeks. Of patients treated for *de novo* LCH, 14/16 (88%) achieved non-active disease by the end of one year of therapy; one patient (6%) had disease progression on therapy and three patients (19%) relapsed within six months of therapy completion. One year PFS was 93%. Among patients treated for recurrent LCH, cytarabine-based regimens induced disease improvement in the first three months of therapy in 13/22 (59%) patients, including 4/6 (67%) risk organ patients. Kaplan-Meier estimated three-year progression-free survival (PFS) for recurrent LCH was 41%, but three-year overall survival was 100%. Risk organ involvement was not associated with lower PFS. Toxicity was limited to neutropenia, fever or infrequent infection requiring hospitalization.

The findings and rationale provided here support prospective evaluation of more rigorous investigation of alternative strategies for front-line LCH therapy. We propose cytarabine as a reasonable first contender to attempt to dethrone vinblastine/prednisone.

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Table 1

Patient characteristics and outcomes.

	<i>De novo</i> LCH (n = 16)	Recurrent LCH (n=22)
Patient age at diagnosis (range/median)	0.4–21 years / 12.8 years	0.4–16.7 years / 1.7 years
Patients with risk organ disease (%)	2 (13)	6 (27)
Patients with pituitary disease (%)	9 (56)	9 (41)
Median time to progression after initial therapy (vinblastine/prednisone)	n/a	0.8 years (0.1–2.8 years)
Cytarabine dose per cycle (median/range)	300–750 mg / 500 mg	450–600 mg / 500 mg
Median follow up post cytarabine	0.9 years	2.8 years
Regimen:		
• Cytarabine (%)	16 (100)	7 (32)
• + vincristine (%)		10 (45)
• + vincristine/prednisone (%)		2 (9)
• + other		3 (14)
Overall survival	100% (1 year)	100% (3 year)
Progression-free survival	93% (1 year)	41% (3 year)
Median time to progression (range)	n/a	1.9 years (0.1–6.6 years)
Toxicity	All evaluable patients (n=26)	
• ANC < $0.5 \times 10^9/l$, n (%)	13 (50)	
• Need for blood product transfusion, n (%)	1 (4)	
• Infusion-associated fever, n (%)	6 (23)	
• Febrile neutropenia, n (%)	5 (19)	
• Infection requiring hospitalization, n (%)	3 (12)	

LCH, Langerhans cell histiocytosis; n/a, not applicable; ANC, absolute neutrophil count