Concerns of Reviewer

1. When should adult LCH be treated? Which are the clinical indications for treatment? Please provide answer and table regarding the indications.

2. Are there any data in the literature regarding relapsed patients?

3. Please correct the grammatical and syntactical errors through the manuscript.

Answers to Reviewer

1. According to Euro-Histio-Net Group, if the patient is symptomatic, treatment recommendations are based on site and extension of disease (multisystem or single system). Moreover the choice of treatment is based on involvement or not involvement of "risk organ" (in particular hematopoietic system, spleen, liver, central nervous system). For details see in attached table 1.

2. About relapsed disease the choice of treatment is based on the same principles as for initial disease (table 1). In particular:
   In relapsed SS-LCH of skin/bone/other the options are: watch and wait (if asymptomatic), local therapy (eventually irradiation), biphosphonate for bone lesions or chemotherapy.
   In relapsed of MS-LCH or multisystem reactivation of SS-LCH systemic therapy. In particular the efficacy of 2-CDA has been reported (Saven et al. 1999).
   Finally in refractory disease especially with CNS involvement cytarabine in combination with 2-CDA has been used (Mc-Clain 2005). Imatinib mesilate showed to play a role in the treatment in some cases (Montella et al 2004, Janku et al 2010). In literature rare aggressive refractory cases has been treated successfully with allogenic hematopoietic stem cells transplantation (Ingram et al 2006, Janku et al 2010). Radiotherapy could be indicated in recurrent or progressive lesions in multifocal o multisystem disease with minor response to standard systemic therapy (Atalar et al. 2010, Heyd et al. 2000).

3. The manuscript has been revised by a professional English language editing company.

Disease category	Treatment
Unifocal LCH	
• Skin	• Local therapy (e.g. topical mustard nitrogen 20% in children • Phototherapy: psolaren plus ultraviolet A (PUVA), narrow band ultraviolet (UV) B.
• Bone	• Intralesional steroid injection (40-160 mg methylprednisolone). • Radiotherapy (in case of neurological deficit, soft tissue involvement).
Multifocal SS-LCH Without "organ risk"	
• SS-LCH (bone lesions)	• Zoledronic acid
• SS-LCH (skin)	• Methotrexate 20 mg per week p.o/i.v. • Azathioprine 2 mg/kg/d p.o. • Thalidomide 100 mg/die p.o. (skin or soft tissue multifocal SS-LCH if symptomatic).
Symptomatic MS-LCH Without "risk organs"	• Cytarabine 100 mg/m2 d1-5 q4w i.v. • Etoposide 100 mg/m2 d1-5 q4w i.v. • Vinblastin/Prednisone ("pediatric like schedule)"
MS-LCH with "risk organs"	• 2-CDA 6 mg/m2 d1-5 q4w s.c./i.v.
PLCH asymptomatic	• Quit smoking

	• Careful observation
PLCH symptomatic	• Sistemic steroids • Chemotherapy in case of progressive disease. • In case of severe respiratory failure or major pulmonary failure consider lung transplantation.

Table 1 Recommendations of first line therapy. (Legend. LCH: Langerhans Cell Histiocytosis, SS-LCH: Single System LCH Langerhans Cell Histiocytosis, MS-LCH: Multi System Langerhans Cell Histiocytosis, P-LCH: Pulmonary Langerhans Cell Histiocytosis, Risk Organs: Hematopoietic system, spleen, liver, central nervous system).