Hematopoietic cell transplantation for Langerhans histiocytosis

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ABSTRACT

Langerhans cell histiocytosis is a rare myeloid neoplasm that primarily affects children. Initial treatment depends on risk stratification, but overall survival is excellent. Patient with high-risk disease with risk organ involvement can experience disease reactivation or refractoriness to front-line therapy. A standard approach is not established in the literature, with different reported strategies, including conventional chemotherapy, MAPK-inhibitors and allogeneic hematopoietic (HCT). Allogeneic HCT is supported by retrospective studies with overall survival ranging from 56 to 77% in the largest series. Disease status at the time of HCT and the conditioning regimen (reduced-intensity conditioning *versus* myeloablative conditioning) correlates with survival and toxicity. Most recently, reduced-intensity conditioning modality has emerged as the preferred option for patients diagnosed with Langerhans cell histiocytosis who require allogeneic HCT.

Keywords: Treatment Failure. Hematopoietic Stem Cell Transplantation. Histiocytosis. Langerhans-Cel. Transplantation Conditioning.

INTRODUCTION

Langerhans cell histiocytosis (LCH) is a rare disease, with an incidence of about five children per 1,000,000 under 15 years old[1]. The clinical presentation is widely heterogeneous, varying from isolated lesions, with no or few symptoms to multisystem involvement and eventually organ dysfunction. The recent description of CD207+ in LCH lesions and the high prevalence of BRAF mutations, leading to activation of the MAPK signaling pathway as a oncogenic driver, support the classification of LCH as a myeloid neoplasia[2,3]. Treatment of LCH is mostly based on a risk-adjusted approach: single lesions may respond to minimal or no treatment, whereas multisystem disease (MS-LCH) requires systemic therapy, mostly vinblastine and corticosteroids first-line therapy[3]. The last trial published by the Histocyte Society showed excellent survival for both low- and high-risk patients, but reactivation occurred in almost 30% of patients[4].

Patients with refractory disease have lower overall survival and risk of long-term health problems, including neurodegeneration, but no standard salvage therapy is stablished[2,4,5]. Since MAPK mutations are commonly found in LCH patients, target therapies with BRAF or MEK/ERK inhibitors are recent alternatives explored for the treatment of recurrent/refractory diseases. Although results are encouraging with high-response rates[6,7], the standard approach has not been established with uncertainties regarding the clonal eradication and treatment duration[8,9]. For those patients with refractory disease or gene-negative LCH, the HCT can be considered as an alternative therapy[10].

The role of allogeneic hematopoietic cell transplantation (HCT) remains a subject of ongoing clinical discussion, as there are currently no randomized clinical trials evaluating its efficacy. Evidence guiding the treatment of high-risk or refractory cases is derived primarily from retrospective analyses.

Steiner et al.[11] explored the management of nine patients with refractory high-risk LCH with allogeneic HCT following a reduced-intensity conditioning (RIC) regimen. Treatment was well tolerated, and transplant-related mortality was lower than for historical myeloablative conditioning (MAC) regimens, with an overall survival of 78%.

In 2015, Veys et al.[12] published results from 87 high-risk patients transplanted from 1990 to 2013. A MAC regimen, typically utilizing total body irradiation or busulfan, were the standard until the early 2000s, after which RIC—largely consisting of fludarabine and melphalan—became the preferred approach. Although the three-year transplant-related mortality rates were comparable between the two groups—21% RIC *versus* 15% MAC—, the risk of recurrence was notably higher in patients receiving RIC regimens (28 *versus* 8%). Despite this disparity in relapse rates, the three-year overall survival remained statistically similar—77% RIC *versus* 71% MAC).

These findings were further supported by Kudo et al.[13] in a retrospective study of 30 patients with refractory LCH, with no significant difference in the five-year overall survival between RIC (56.8%) and MAC (63.6%) modalities.

Disease status at the time of HCT has emerged as the primary prognostic factor; patients who achieve remission or partial remission prior to the procedure demonstrate a five-year overall survival of 100%, whereas those with active disease at the time of transplantation had a significantly lower survival rate of 54.5%. Conversely, factors such as the type of donor—frequently unrelated—and the source of stem cells, including bone marrow and umbilical cord blood, do not appear to exert a significant impact on overall survival rates[9–14].

There is no evidence for autologous HCT in LCH, mostly case reports based (Table 1 and 2).

Table 1. Hematopoietic cell transplant type.

	Autologous	Allogeneic
Localized (or RO -)	Not indicated	Not indicated
Multisystem and risk organ involvement (MS RO +)		
Recurrent/refractory	Not indicated	Indicated

RO: risk organ; MS: multisystem. Source: Elaborated by the authors.

Table 2. Hematopoietic cell transplant indications, graft, and stem cell source.

	Indication	Allogeneic
Multisystem and risk organ involvement (MS RO+)	Recurrent/refractory to first line or savage therapy	MSD > MUD > MMD Bone marrow

RO: risk organ; MS: multisystem; MSD: matched sibling donor; MUD: matched unrelated donor; MMD: mismatched donor. Source: Nr and Kinderkrebsforschung[15].

The role of HCT for the treatment of relapsed/refractory pediatric LCH under investigation in the most recent clinical trial (LCH-IV) conducted by the Histiocyte Society[15], with no results published so far. A RIC HCT with alemtuzumab, fludarabine, and melphalan is an alternative considered for MS-LCH patients with risk organ involvement and refractory to first-line or to salvage therapy. Although RIC procedures have been preferred in recent years, there is no clear survival advantage of RIC *versus* MAC HCT. Considering LCH as myeloid neoplasia, myeloablative conditioning regimens with reduced toxicity protocols, including the addition of thiotepa or treosulfan to fludarabine and melphalan, are reasonable alternatives[10] (Table 3 and 4).

Table 3. Conditioning.

HCT	Conditioning
RIC	Day -8 to -4: Alemtuzumab 0.2 mg/kg Day -7 to -3: Fludarabine 30 mg/m^2 Day -2: Melphalan 140 mg/m^2 Day -1: Rest Day 0: Stem cell infusion Day +8: GSCF 5 mcg/kg/day

HCT: hematopoietic cell transplant; RIC: reduced-intensity conditioning; GCSF: granulocyte-colony stimulating factor. Source: Nr and Kinderkrebsforschung[15].

Table 4. Graft-*versus*-host-disease prophylaxis.

Hematopoietic cell transplant	Graft-*versus*-host-disease prophylaxis
	Day -3: Cyclosporine Day -3: Mycophenolate mofetil, if mismatched donor

Source: Nr and Kinderkrebsforschung[15].

CONFLICT OF INTEREST

Nothing to declare.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable.

AUTHORS' CONTRIBUTIONS

Substantive scientific and intellectual contributions to the study: Netto GZ and Bom APKP. **Conception and design:** Netto GZ and Bom APKP. **Analysis and interpretation of data:** Netto GZ and Bom APKP. **Technical procedures:** Netto GZ and Bom APKP. **Statistics analysis:** Netto GZ and Bom APKP. **Manuscript writing:** Netto GZ and Bom APKP. **Final approval:** Netto GZ.

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DECLARATION OF USE OF ARTIFICIAL INTELLIGENCE TOOLS

The authors declare that no artificial intelligence tools were used in the preparation, writing, data analysis, or review of this manuscript.

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