Safety and efficacy of anakinra in hemophagocytic lymphohistiocytosis associated with acute leukemia

Hemophagocytic lymphohistiocytosis (HLH) is a rare, life-threatening condition in which immune hyperactivation and dysregulation results in a cytokine storm. HLH may be primary (due to underlying genetic mutations) or secondary to triggers such as infections, autoimmune/autoinflammatory disorders, and malignancies (HLH-M).[1] In over 90% of cases, HLH-M is driven by a hematologic malignancy, with lymphoma the most common trigger.[2] The clinical features of HLH-M may be driven by the hematologic malignancy itself, infection secondary to the immunosuppressed state, loss of immune homeostasis, or a combination of these.

The association between acute leukemia and HLH is less well-recognized despite a few reported cases.[3,4] A single case series described HLH-M with acute myeloid leukemia (AML).[4] In keeping with the high mortality associated with HLH-M, the overall survival (OS) for such patients was significantly lower than age-, disease- and treatment-matched controls without HLH. Current recommended treatments for HLH-M include steroids, intravenous immunoglobulin (IVIG) and etoposide/ciclosporin-containing regimens.[5] In contrast, the recommended treatment for HLH-macrophage activation syndrome (MAS), (seen in rheumatologic disease) is anti-IL1-directed therapy such as anakinra. In 2021, the UK approved the use of anakinra to treat HLH of any cause; however, the safety and efficacy data of anakinra in HLH-M remains limited.[6]

We report a retrospective review of all patients diagnosed with HLH and AML or acute lymphoblastic leukemia (ALL) in a single London tertiary referral center (University College London Hospitals NHS Foundation Trust [UCLH]), between 1 January 2019 and 31 December 2022, their clinical course, and successful and safe therapy with anakinra-containing regimens. Patients (or their relatives if deceased) provided written consent. The UCLH Hematology Department registered the project as a service evaluation.

To define patients with a diagnosis of HLH, we analyzed electronic records of all patients referred to the UCLH HLH multidisciplinary meeting (MDM), a national framework for case discussions among hematology, rheumatology, infectious disease, and intensive care (ICU) clinicians. We cross-referenced patients thus identified with all adult and teenage patients treated with AML and ALL on local disease-specific registries. This identified 468 patients with acute leukemia, of whom 13 (2.8%) were diagnosed with HLH. Clinical and laboratory data were collected using the electronic health records (Table 1). For diagnostic purposes, we utilized HScores (comprising laboratory and clinical parameters providing an HLH probability for each patient) using laboratory data.[7] HLH was diagnosed in patients with a clinical suspicion of HLH and an HScore >169.

Median age at time of HLH diagnosis was 37 years (range 16-74). Four patients were female and 8 were male. Two patients (15%) had standard risk B-ALL. Eleven patients (85%) had AML; of these, 4 (36%) had favorable risk (inversion 16 or *NPM1* mutated), whilst 7 (64%) had adverse risk (MLL rearrangement, myeloid sarcoma, therapy-related AML, and AML with myelodysplastic syndrome-related changes). Four patients were diagnosed at time of leukemia presentation, 6 during induction chemotherapy, and 3 in consolidation. Ten patients (77%) had active leukemia at the time of their HLH diagnosis; only 3 (27%) were in remission.

Patients were treated with various types of immunosuppressive therapy (IST). Twelve (92%) received anakinra, 3 (17%) of whom had anakinra monotherapy whilst the remainder had anakinra with steroids (38%), steroids and IVIG (15%), or steroids, IVIG and etoposide (8%). One patient (8%) had steroids and IVIG alone. Anakinra was given intravenously in 11 patients and subcutaneously in one. The mean daily dose was 4.6 mg/kg. Eleven patients (92%) were neutropenic prior to starting anakinra; 8 patients were severely neutropenic with an absolute neutrophil count $<0.5x10^9$/L. All patients required ICU input during their HLH treatment. Eight (62%) were admitted to ICU on diagnosis with HLH and required ventilatory and/or vasopressor support; the remainder were reviewed by ICU outreach. In all, 92% patients had an initial rapid clinicopathologic response following IST, becoming afebrile, with a reduction in oxygen requirement and hemodynamic stability seen within 24-72 hours. One patient (8%) had a reduction in oxygen requirement following anakinra monotherapy but continued to spike temperatures and required oxygen for two weeks. However, this patient was positive for COVID-19 on PCR and pneumonitis on chest radiology. Another patient (8%) had an initial clinical response to anakinra, methylprednisolone and IVIG triple therapy, but displayed subsequent rapid deterioration in the context of pseudomonal infection, and required readmission to ICU and continued anakinra. The patient nevertheless died of multiorgan failure.

Nine patients (69%) had no HLH recurrence following IST. Three (23%) had an initial clinical response to IST but had subsequent biochemical and clinical relapse of HLH. These patients all had relapsed/refractory disease on HLH recurrence; no patient had relapsed HLH without contemporaneous leukemia relapse. One of these subsequently received etoposide and further steroids resulting in resolution of clinical HLH, despite underlying refractory AML. The second was re-challenged with anakinra and methylprednisolone alongside venetoclax-azacitidine as

second-line AML treatment with a clinical response to HLH treatment, although subsequently therapy was withdrawn due to refractory leukemia. The third had refractory myeloid sarcoma and continued maintenance prednisolone alongside palliative care.

Patient outcomes are shown in Figure 1. Only one (8%) patient died directly from HLH. Eight (62%) remain in remission from leukemia at the end of the study period. Three of these (23%) were in remission following chemotherapy only. Three other patients (23%) had relapsed leukemia following their HLH diagnosis but are now in remission post allogeneic stem cell transplant. Three of the 6 patients (50%) who had relapsed leukemia had contemporaneous HLH relapse. Two patients had allogeneic transplant for unfavorable risk disease; both are in remission post allogeneic transplant. Three patients (23%) died of refractory leukemia, all having unfavorable risk disease at presentation. A fourth patient (8%) has refractory therapy-related AML following initial treatment for follicular lymphoma and is currently receiving palliative care. Another patient (8%) is in remission from leukemia but remains on dialysis for end-stage renal failure secondary to HLH. Of the 3 patients who were in remission from leukemia at the time of HLH diagnosis, one subsequently had an allograft for high-risk disease, and one died from HLH. The third patient had developed HLH secondary to acute COVID-19 infection, and remained in remission following HLH treatment.

Although the link between HLH and lymphoma is well characterized, data on HLH in the context of acute leukemia are limited. In this case series, 2.8% of the patients treated with acute leukemia developed HLH, which is similar to the figure of 3% for lymphoma quoted elsewhere.[8] The majority (92%) of patients had microbiologic or radiologic evidence of infection on HLH diagnosis. However, many such infections involved organisms not classically associated with HLH, e.g., rhinovirus and *Streptococcus oralis*.[9]

We hypothesize that the clinical features of HLH in these patients may be driven by a combination of the underlying leukemia, chemotherapy and infection resulting in immune dysregulation. The central role of leukemia in the

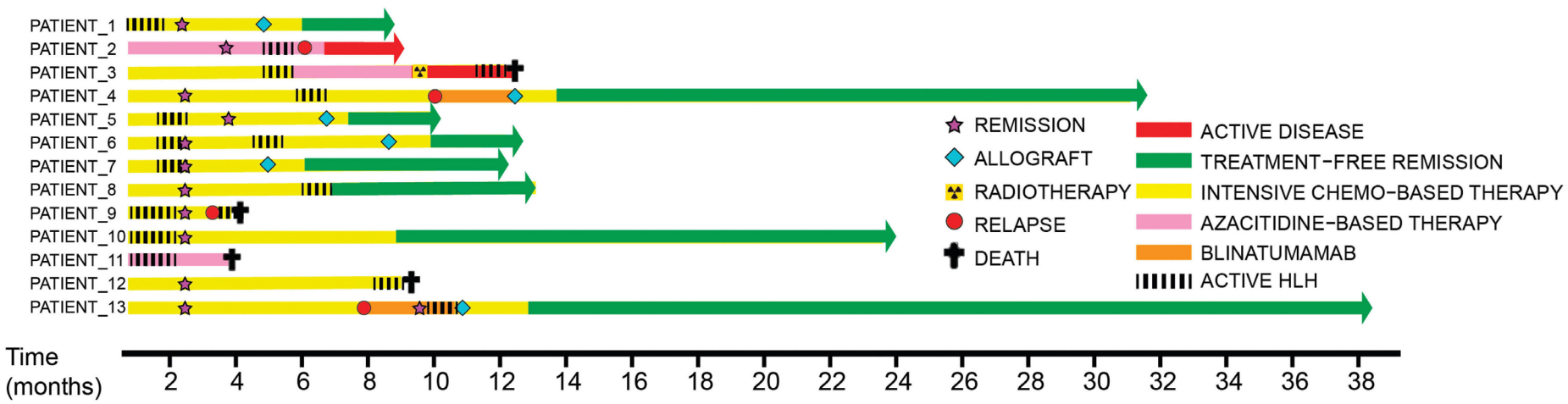

Figure 1. Treatment course and outcomes per patient over time. HLH: hemophagocytic lymphohistiocytosis.

Table 1. Hemophagocytic lymphohistiocytosis diagnostic criteria in the cases from the study.

Parameter	Values
Median H score (range)	214 (181-299)
Probability of HLH, %	93-96
Peak serum ferritin, mcg/L, median (range) [reference <500]	79,889 (7,197-488,068)
Serum triglyceride, mmol/L, median (range) [reference <1.5]	3.7 (1.8-8.5)
Hepatosplenomegaly, N (%)	5 (38)
BM evidence of hemophagocytosis, N (%) Yes No Not done	 7 (61) 4 (36) 2 (15)
Evidence of infection, N (%) Bacterial, N (%) Viral, N (%) Radiological, N (%)	12 (92) 4 (31) (*E. Coli, Klebsiella, pseudomonas, streptococcus oralis*) 3 (23) (COVID-19: N=2; Rhinovirus: N=1) 3 (23) (arm abscess: N=1; consolidation on HRCT: N=2)

BM: bone marrow; HLH: hemophagocytic lymphohistiocytosis; HRCT: high-resolution computed tomography; N: number.

pathogenesis of HLH-M in these cases is highlighted by the relapse of HLH occurring alongside leukemia relapse in 3 of the 6 patients who relapsed their leukemia. One patient developed HLH whilst in remission from leukemia and remained in remission from both leukemia and HLH without an allograft; however, as HLH occurred in the context of acute COVID-19 infection, which is known to be associated with HLH/MAS, it is possible that COVID-19 rather than leukemia was the key driver in this context.

All patients in our cohort required ICU support. However, compared to existing literature, treatment responses and outcomes were good, with an OS rate of 62% in our cohort. Only one patient died of HLH alone; the remaining 3 patients who died during the study period died of relapsed-refractory leukemia. This contrasts with other studies with higher mortality rates; Tamamyan *et al.*[4] reported an OS rate of 15% in 13 patients with HLH-M. Delavigne *et al.*[3] reported a 3-month mortality rate of 36% in AML patients presenting with HLH during induction compared to our figure of 23% for this period.

Twelve patients (92%) in our cohort received anakinra as part of their therapy for HLH-M; in 9 patients, this was used alongside steroids and/or IVIG. We recommend using intravenous anakinra since this has been shown to be more effective than subcutaneous forms in critically unwell patients.[10] Anakinra use allows a reduction in the amount and duration of steroids required, which is critical given the known toxicity of high-dose steroids, including further immunosuppression and risk of opportunistic infections.[11] Our data show treatment with anakinra appears safe in the context of neutropenia. We recommend early discussion of patients with possible HLH-M in an MDM setting, and early use of IV anakinra, IVIG and methylprednisolone first-line. The use of etoposide is reserved for refractory cases.

We believe this is the first case series demonstrating effective treatment and high OS of HLH-M patients with concurrent leukemia diagnosis using anakinra. We hypothesize that early treatment with anakinra alongside other immunosuppression may explain the trend towards improved outcomes in our cohort. Further work is needed to characterize which patients are at increased risk of developing HLH to ensure its early detection and treatment.

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Contributions

HA carried out data collection and analysis, and wrote the manuscript. EP supervised the study and provided support in writing the manuscript. SG, JM, JO and AW provided additional supervision and support in writing the manuscript.

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Data-sharing statement

Original data and protocols can be obtained by contacting the corresponding authors.

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