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Review Article

Iron Overload, Heme Oxygenase-1 Expression and Drug Resistance in Acute Leukemia

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Summary

Serum ferritin before transplantation predicts death with unusual reliability, and it is routinely read as a measure of iron overload. The pattern of that mortality, and what direct iron measurement shows, suggest a substantial part of the signal is inflammation rather than iron, which decides whether chelation could help.

Objectives: To review the published evidence on iron overload and heme oxygenase-1 expression in acute leukaemia: what raised ferritin predicts, whether it reflects iron burden, how the enzyme contributes to chemoresistance, and where the two lines of evidence meet.

Material and Methods: Narrative review of prospective and retrospective transplant cohorts, imaging studies, laboratory work and systematic reviews indexed in PubMed and the major haematology journals. Studies were eligible if they reported the association between iron status or heme oxygenase-1 expression and outcome or drug sensitivity in a defined acute leukaemia or myelodysplastic syndrome population. No new patient data were generated and no patients were recruited; every estimate quoted is one published by the original investigators.

Results: In a prospective multicentre study of 298 allogeneic transplant recipients using a ferritin threshold of 1,500 micrograms per litre, overall survival (HR 2.5, 95% CI 1.5-4.1, $p = 0.0005$) and progression-free survival (HR 2.4, 95% CI 1.6-3.8, $p < 0.0001$) were inferior above the cut-off, with excess mortality from both higher relapse (HR 2.2) and higher non-relapse mortality (HR 3.1), the latter driven by infection-related death (HR 3.9, 95% CI 1.6-9.7, $p = 0.003$). Neither the incidence nor the severity of graft-versus-host disease was associated with ferritin. In a prospective imaging study, ferritin correlated with estimated liver iron concentration at $r = 0.75$, largely dependent on transfusion history, while labile plasma iron elevation was rare and hepcidin was appropriately raised. In laboratory work, a cytarabine and daunorubicin-resistant cell line showed high heme oxygenase-1 expression, and silencing the gene restored chemosensitivity with reduced hypoxia-inducible factor 1- α and glucose transporter 1, increased caspase-3 and caspase-8 and decreased BCL-2.

Conclusion: Ferritin is a robust prognostic marker and a poor measure of iron, and the mortality it predicts is infectious rather than the organ toxicity iron overload would cause. Heme oxygenase-1 sits at the junction of the two, being both an iron-releasing enzyme and a stress-response gene conferring resistance.

Abbreviations: AML – Acute Myeloid Leukaemia, ALL – Acute Lymphoblastic Leukaemia, MDS – Myelodysplastic Syndrome, HO-1 – Heme Oxygenase-1, NRF2 – Nuclear Factor Erythroid 2-Related Factor 2, HIF-1 α – Hypoxia-Inducible Factor 1-Alpha, GLUT1 – Glucose Transporter 1, LIC – Liver Iron Concentration, LPI – Labile Plasma Iron, SF – Serum Ferritin, NRM – Non-Relapse Mortality, GVHD – Graft-Versus-Host Disease, alloSCT – Allogeneic Stem Cell Transplantation, ROS – Reactive Oxygen Species.

Keywords: Acute Leukaemia; Iron Overload; Heme Oxygenase-1; Serum Ferritin; Chemoresistance

Introduction

Patients with acute leukaemia receive repeated red cell transfusions during induction and consolidation, and each unit delivers iron the body has no regulated route to excrete [1,2]. Transfusional iron accumulates in liver, heart and endocrine tissue, and in chronically transfused populations it causes organ failure unless chelated [3,4].

Iron status in leukaemia is assessed almost universally by serum ferritin, which is inexpensive and widely available [5,6]. Raised ferritin before transplantation has been associated with poorer survival in numerous retrospective analyses and in prospective studies, and it is often

described as a surrogate measure of iron overload [1,7,8].

Ferritin is not, however, an iron assay. It rises during inflammation and macrophage activation as well as with iron loading [9,10], and both processes are present in a patient with active leukaemia receiving cytotoxic therapy. Separating the two matters because chelation addresses one and not the other [2,11].

Heme oxygenase-1 connects these questions. The enzyme degrades heme into biliverdin, carbon monoxide and ferrous iron, so it is a source of intracellular iron; it is also a canonical oxidative stress response gene overexpressed in acute myeloid leukaemia and implicated in resistance to chemotherapy [12,13,14].

Material and Methods

Search strategy: PubMed and the archives of the major haematology and transplantation journals were searched for studies of iron status and heme oxygenase-1 in leukaemia. Search terms combined acute leukaemia and myelodysplastic syndrome with serum ferritin, iron overload, transfusion burden, liver iron concentration, labile plasma iron, chelation, heme oxygenase-1 and chemoresistance. Reference lists of retrieved cohorts and laboratory studies were screened by hand.

Eligibility: Studies were included if they reported the association between iron status or heme oxygenase-1 expression and clinical outcome or drug sensitivity in a defined acute leukaemia or myelodysplastic syndrome population. Laboratory studies in cell lines and murine models are cited where they establish mechanism and are identified as such.

Data extraction and handling: Design, cohort size, method of iron assessment, threshold applied and reported effect estimates were extracted as published. The method of iron assessment is stated alongside every estimate, because the central question of this review is whether ferritin measures what it is taken to measure. No pooling or re-analysis was performed and no patient-level data were obtained. Figures 1 to 4 and Tables 1 to 3 reproduce published values only. This is a narrative synthesis and was not registered as a systematic review.

Results

What a raised ferritin predicts: A prospective non-interventional study across twenty centres reported outcomes for 298 patients with acute leukaemia, lymphoma or myelodysplastic syndrome receiving a first matched sibling allograft, using a threshold of 1,500 micrograms per litre set at the cohort median [9]. Above that value, overall survival (HR 2.5, 95% CI 1.5 to 4.1, $p = 0.0005$) and progression-free survival (HR 2.4, 95% CI 1.6 to 3.8, $p < 0.0001$) were inferior [9].

Excess mortality arose from both directions. Relapse incidence was higher (HR 2.2, 95% CI 1.2 to 3.8, $p = 0.007$) and so was

non-relapse mortality (HR 3.1, 95% CI 1.5 to 6.4, $p = 0.002$), the latter driven by significantly higher infection-related mortality (HR 3.9, 95% CI 1.6 to 9.7, $p = 0.003$) (Figure 1) [9].

Retrospective work agrees on direction and magnitude. Raised pretransplantation ferritin was strongly associated with lower overall and disease-free survival, an association restricted on subgroup analysis to patients with acute leukaemia or myelodysplastic syndrome, with an absolute difference of 37 per cent in five-year survival between highest and lowest quartiles in the myelodysplastic group [7,8].

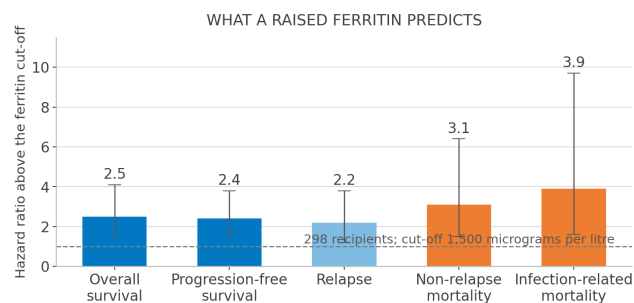


Figure 1: Hazard ratios above the ferritin threshold in 298 transplant recipients [9]

The endpoint it does not predict: In the same prospective study, neither the incidence nor the severity of acute or chronic graft-versus-host disease was associated with ferritin levels (Figure 2) [9]. That negative result is informative rather than incidental.

Graft-versus-host disease is the alloimmune complication of transplantation, whereas infection reflects the depth and duration of immune incompetence [15,16]. A marker tracking infection but not alloreactivity is pointing at host defence rather than at donor immunity, which is consistent with either iron-mediated impairment of neutrophil and macrophage function or with underlying inflammation [11,17].

Systematic review of ferritin and outcome in acute myeloid leukaemia reports the same pattern, with infection prominent among causes of death in patients above the threshold and an association between pre-transplant levels and relapse susceptibility that was not consistent across all studies examined [18].

Ferritin measured at diagnosis rather than before transplantation carries prognostic weight as well, which argues that at least part of the signal precedes transfusional loading [23]. A patient has received few units at that point, so a raised value at presentation is more plausibly disease-related inflammation than accumulated iron [17,23].

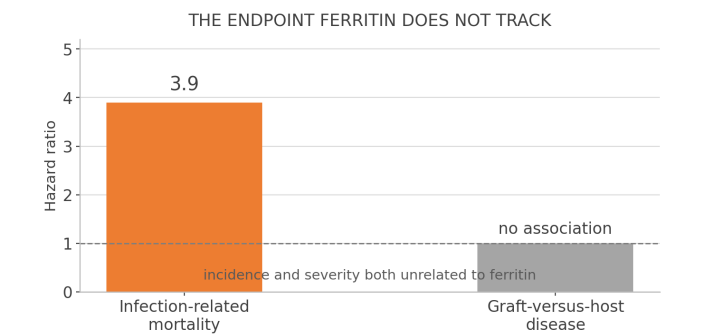


Figure 2: Infection-related mortality against graft-versus-host disease in the same cohort [9]

Study	n	Method	Principal reported finding
Armand et al. 2007 [7]	Cohort	Serum ferritin	Lower survival; 37% quartile difference in myelodysplasia
Alessandrino et al. 2010 [8]	Cohort	Ferritin and transfusion burden	Ferritin independent; transfusion count not
Armand et al. 2011 [10]	Prospective	Magnetic resonance imaging	Labile plasma iron rare; hepcidin appropriate
Wei et al. 2015 [13]	64	Expression and silencing	Enzyme silencing restores chemosensitivity
Penack et al. 2020 [9]	298	Prospective, multicentre	Infection-related mortality hazard ratio 3.9
Zhang et al. 2022 [19]	Laboratory	Co-culture and murine	Enzyme drives escape from natural killer cells

Table 1: Principal studies reviewed, with method and the finding as reported by the original investigators

What direct measurement shows: A prospective study used hepatic and cardiac magnetic resonance imaging to estimate iron burden in consecutive adults with acute leukaemia or myelodysplastic syndrome scheduled for myeloablative transplantation, alongside labile plasma iron and hepcidin in plasma and urine [10]. Ferritin correlated strongly with estimated liver iron concentration at $r = 0.75$, and that correlation was mostly dependent on prior transfusion history (Figure 3) [10].

Two further findings complicate the simple reading. Labile plasma iron elevation, which is the fraction held responsible for tissue injury through catalysis of free radical formation, was rare [10]. And serum hepcidin was appropriately elevated in patients with hepatic iron overload, indicating that the regulatory response to iron loading was intact rather than deranged [10].

Regression calibration in that study supported the hypothesis that raised pre-transplant liver iron concentration is significantly associated with inferior post-transplant survival [10], so iron burden does carry prognostic weight independently. What the data do not establish is that the ferritin signal is wholly attributable to it [2,9,10].

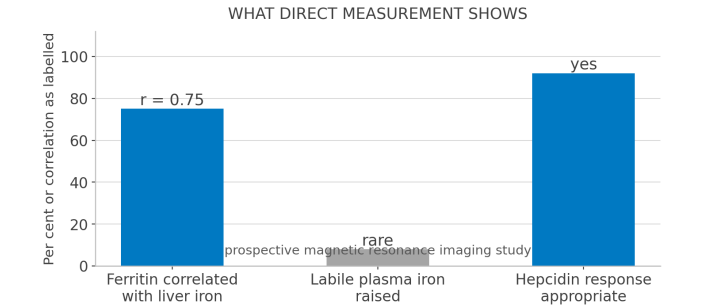


Figure 3: Findings from direct iron measurement in a prospective imaging study [10]

The enzyme and chemoresistance: Heme oxygenase-1 has been implicated in acquired resistance in solid tumours, and its role in acute myeloid leukaemia was examined by comparing marrow or blood from newly diagnosed ($n = 26$), relapsed ($n = 10$) and remitted patients ($n = 18$) against healthy donors ($n = 10$), with silencing experiments in cell lines (Figure 4) [13].

A cytarabine and daunorubicin-resistant line expressed markedly higher enzyme messenger RNA and protein than its sensitive parent, and downregulating the gene significantly enhanced sensitivity to chemotherapy. Hypoxia-inducible factor 1-alpha and glucose transporter 1 fell, caspase-3 and caspase-8 rose, and BCL-2 decreased [13]. Overexpression of all three genes was associated with poor response in patients [13].

Independent work established that the enzyme underlies resistance of leukaemic cells to tumour necrosis factor-induced apoptosis [12], and simultaneous targeting of the enzyme and of hypoxia-inducible factor 1-alpha has been shown to sensitise cells to cytarabine [20]. Enzyme expression is regulated through nuclear factor erythroid 2-related factor 2 among other pathways [14,21].

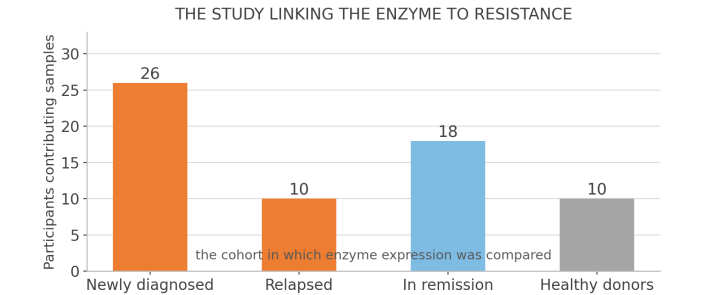


Figure 4: Composition of the cohort in which enzyme expression was compared [13]

Measure	What it reflects	What it predicts
Serum ferritin	Iron stores and inflammation together	Survival, relapse, infection death [7,9]
Transfusion burden	Iron delivered	Not independent of ferritin [8]
Liver iron by imaging	Tissue iron directly	Inferior survival [10]
Labile plasma iron	The injurious fraction	Rarely elevated [10]
Hepcidin	Regulatory response	Appropriately raised [10]

Table 2: Measures of iron status and what each captures

Iron after transplantation, not only before it: Ferritin does not stabilise once conditioning is complete. Levels rise further in the months after transplantation, peaking between one and six months, and post-transplant iron overload carries its own prognostic weight [24,26]. Management of iron burden in this population has accordingly been addressed as a question extending beyond the pre-conditioning measurement [25,27].

Hepcidin behaviour after transplantation reflects erythropoietic activity as well as iron status [28], which complicates interpretation during engraftment precisely when transfusion requirement is highest. That temporal complexity is one reason a single pre-conditioning value is a convenient rather than a complete assessment [10,24].

Iron in cancer biology more broadly: The relationship between iron and malignancy is not confined to transfusional loading. Iron requirements of proliferating cells, and the pathways tumours use to acquire it, have been reviewed as a therapeutic target in their own right [29]. Ferroptosis, an iron-dependent non-apoptotic cell death, was characterised as a distinct mechanism [30] and is the process the enzyme modulates in both directions [22].

Oxidative stress links this to leukaemia genetics. Internal tandem duplication of FLT3 raises reactive oxygen species production with increased DNA damage and misrepair [31], and cell lines carrying that lesion show upregulated enzyme and nuclear factor erythroid 2-related factor 2 expression [22,31]. Whether iron overload compounds that burden in patients has not been established [29,32].

Organ consequences of iron loading are best characterised in the heart, where both deficiency and overload impair function [32]. In leukaemia, cardiac risk is dominated by anthracycline exposure, so an additional iron-mediated contribution would be difficult to isolate without direct imaging [10,32,33].

Question	Current answer	Evidence quality
Does raised ferritin predict death?	Yes, robustly	Prospective multicentre [9]
Does it reflect iron burden?	Partly	Imaging correlation $r = 0.75$ [10]
Is the injurious iron fraction raised?	Rarely	Direct measurement [10]
Does the enzyme confer resistance?	Yes in vitro	Silencing experiments [13,20]
Does chelation improve survival?	Unknown	No randomised trial [2]

Table 3: What is established and what is not across the two lines of evidence

Discussion

Ferritin is an excellent prognostic marker and a poor iron assay, and the literature has tended to treat those as one property. Above 1,500 micrograms per litre, survival, progression-free survival, relapse and non-relapse mortality all worsen, with hazard ratios between 2.2 and 3.1 [9]. That predictive performance is not in doubt.

What the data do not establish is that iron is the operative agent. Ferritin rises with inflammation and macrophage activation as well as with iron loading [9,17]; the mortality it predicts is infectious rather than the cardiac and hepatic failure that iron overload causes in chronically transfused populations [3,4,9]; and direct measurement found the injurious labile fraction rarely elevated with an intact hepcidin response [10].

Why the distinction decides the intervention

If raised ferritin marks iron overload, chelation should improve outcome, and the absolute survival difference of 37 per cent between ferritin quartiles in myelodysplasia would make that a large prize [7]. If it largely marks inflammation and disease activity, chelation would remove the marker without touching the process, and the resources would be better directed at infection prevention [2,9].

The evidence does not currently settle this. Whether iron chelation can safely and effectively reverse iron overload in patients continuing to receive transfusions, and whether that would translate into improved survival, has been identified as requiring prospective randomised testing rather than assumed [2]. Retrospective association cannot answer it because the confounding runs in the direction of the hypothesis.

Where the enzyme fits

Heme oxygenase-1 is the point at which the two halves of this literature meet, and it is dual in a way that resists simple interpretation. It liberates ferrous iron from heme, so its induction raises the intracellular labile pool; it is also induced by oxidative and

inflammatory stress, so its expression marks the same processes that raise ferritin [12,14,21].

Its effect on cell death is correspondingly double-edged. Iron released by the enzyme can drive ferroptosis through ferritin degradation, while the same enzyme protects leukaemic cells from oxidative injury and from immune clearance, with the balance depending on the metabolic state of the cell and its microenvironment [14,19,22]. Overexpression has been shown to drive escape from natural killer cell cytotoxicity through suppression of an activating ligand [19].

Study limitations

The limitations belong to the underlying literature. Ferritin thresholds differ between studies, with 1,000 and 1,500 micrograms per litre both in use, and cut-offs set at cohort medians are not transferable [9,18,23]. The prospective imaging study enrolled a modest number of patients and excluded some who could not tolerate the scan, which may select against the sickest [10]. Most evidence on transplant outcome is retrospective and single-institution, and confirmatory prospective trials have been called for repeatedly [2,7]. Laboratory findings on the enzyme derive largely from cell lines, with patient sample numbers in the tens [13,20]. And ferritin is measured at a single pre-conditioning timepoint while both iron burden and inflammation change substantially through transplantation [18,24].

Two gaps deserve naming. No randomised trial has tested whether chelation before transplantation improves survival, so the therapeutic inference from a robust prognostic marker remains untested [2,10]. And no study reviewed here reports outcome stratified simultaneously by ferritin and by an independent inflammatory marker, which is the analysis that would separate the two contributions [9,17].

Conclusion

Serum ferritin above 1,500 micrograms per litre before allogeneic transplantation predicts inferior overall and progression-free survival at hazard ratios of 2.5 and 2.4, with excess mortality from both relapse and non-relapse causes, the latter driven by infection at a hazard ratio of 3.9. Graft-versus-host disease shows no association. Direct measurement complicates the iron interpretation: ferritin correlates with liver iron at $r = 0.75$ largely through transfusion history, yet labile plasma iron is rarely raised and the hepcidin response is intact. Heme oxygenase-1 links the two lines of evidence, releasing iron from heme while also acting as a stress-response gene whose silencing restores chemosensitivity and reduces hypoxia-inducible factor 1- α and BCL-2. Whether the ferritin signal is iron, inflammation or both determines whether chelation would help, and that question has not been tested. Ferritin measured

at diagnosis, before meaningful transfusion has occurred, already carries prognostic weight, which points toward inflammation as a substantial part of the signal [23,34].

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Conflict of Interest

The authors declare no competing interests.

Ethics Statement

This article reviews previously published studies only. No new patient data were collected and no participants were recruited, so ethical approval was not required.

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