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Three-Month Follow-Up of High-Dose Intravenous Iron Monotherapy for Cancer-Related Anemia in an ESA-Free Oncology Setting: A Real-World Cohort Study

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Abstract

Background

We extended our prior 1-month report to evaluate 3-month hemoglobin (Hb) outcomes, transfusion avoidance, and follow-up feasibility after high-dose intravenous iron monotherapy for cancer-related anemia in an erythropoiesis-stimulating agent (ESA)-free oncology setting.

Methods

This retrospective single-center cohort included adults with active solid malignancy who received high-dose intravenous ferric carboxymaltose or ferric derisomaltose monotherapy. Follow-up was evaluated at prespecified 1-month and 3-month windows. The primary analysis assessed Hb change from baseline to 3 months in evaluable non-transfused patients; transfusion avoidance was summarized descriptively.

Results

The cohort comprised 65 patients. In-window Hb was available in 62 patients at 1 month and 42 at 3 months; 27 formed the non-transfused 3-month primary analysis set. Mean Hb increased from 9.01 ± 1.47 g/dL at baseline to 11.09 ± 1.67 g/dL at 3 months (mean change + 2.08 ± 1.72 g/dL; $p < 0.001$). Hb improvement was greater at 3 months than at 1 month, with a further paired increase among non-transfused patients (+ 0.52 ± 1.27 g/dL; $p = 0.043$). Observed transfusion avoidance was 81.5% at 1 month and 72.3% across available in-system follow-up within 3 months. Attrition was substantial: 23 patients were non-evaluable for 3-month Hb because of transfer/community follow-up (n = 15), death (n = 7), or data cutoff/window not reached (n = 1).

Conclusions

In this ESA-free oncology setting, high-dose intravenous iron monotherapy was associated with 3-month Hb improvement in evaluable non-transfused patients, with descriptively high observed transfusion avoidance and substantial attrition.

Introduction

Cancer-related anemia is a common clinical problem in patients with solid malignancies and is associated with fatigue, impaired physical functioning, reduced quality of life, and reliance on red blood cell (RBC) transfusion[1, 2]. In routine oncology care, anemia is often multifactorial, reflecting bleeding, inflammation-associated functional iron restriction, nutritional compromise, anticancer treatment, and marrow suppression; however, iron-restricted erythropoiesis remains a clinically actionable component

for clinical oncologists managing ongoing anticancer therapy and supportive care, because anemia management intersects with treatment continuity, symptoms, and day-to-day function[1, 2].

In the Japanese practice environment examined here, erythropoiesis-stimulating agents (ESAs) are not used for chemotherapy-induced anemia. Intravenous iron and RBC transfusion therefore remain the principal supportive options when anemia worsens, although transfusion provides only immediate correction and adds visit burden and resource use[3]. Modern high-dose intravenous iron formulations, including ferric carboxymaltose (Ferinject®, Zeria Pharmaceutical Co., Ltd., Tokyo, Japan) and ferric derisomaltose (MonoVer®, Nippon Shinyaku Co., Ltd., Kyoto, Japan), allow rapid iron repletion in one or a few visits, which may be clinically relevant during active cancer care[2]. Prior studies suggest that intravenous iron can improve hemoglobin (Hb) outcomes and may reduce transfusion requirements even without concomitant ESA therapy[4–6].

We previously reported 1-month outcomes after high-dose intravenous iron monotherapy in the same ESA-free oncology setting. That report showed an early Hb rise, high observed transfusion avoidance, and short-term safety[7]. However, the analysis was limited to approximately 1 month after treatment. Whether Hb response is maintained or deepened, whether observed transfusion avoidance remains describable over a longer interval, and whether safety and laboratory follow-up remain feasible at a 3-month landmark remained unresolved[7]. These questions are important in routine oncology practice, where death, transfer, community-based follow-up, or discontinuation of hospital visits can limit evaluable short-to-intermediate follow-up[8].

Therefore, this study extends our prior 1-month report by evaluating an updated real-world cohort of adults with active solid malignancy treated with high-dose intravenous iron monotherapy in an ESA-free Japanese oncology setting. We evaluated Hb change and maintenance through 3 months, observed transfusion avoidance, safety, and follow-up feasibility/attrition at the prespecified 3-month landmark as a pragmatic endpoint in routine care.

Methods

Study design and setting

This retrospective single-center cohort study was conducted at University of Toyama Hospital, a tertiary referral center in Japan, using routine electronic medical records from medical oncology and palliative/supportive care practice. The study analyzed an updated real-world cohort extending our prior 1-month series to 3-month follow-up after high-dose intravenous iron monotherapy for cancer-related anemia. In this ESA-free Japanese oncology setting, intravenous iron and red blood cell (RBC) transfusion were the principal supportive-care options for anemia management.

Patients and eligibility

Eligible patients were adults with active solid malignancy who received ferric carboxymaltose or ferric derisomaltose for anemia judged by the treating physician to be cancer-related. This definition included chemotherapy-associated anemia and anemia managed during radiotherapy, pretreatment care, or best supportive care. Patients were identified from institutional treatment records and chart review. The index date was the first administration date of the initial high-dose intravenous iron course. Patients were included irrespective of later RBC transfusion, which was treated as part of the post-index clinical course. Patients were excluded only if the index treatment could not be established or baseline hemoglobin (Hb) data were unavailable. Follow-up was assessed through 3 months after the index date.

Treatment exposure

Treatment exposure was high-dose intravenous elemental iron administered as ferric carboxymaltose or ferric derisomaltose at the discretion of the treating oncologist. Ferric carboxymaltose was generally administered in 500-mg aliquots, whereas ferric derisomaltose was administered as a single high-dose infusion. When the initial course comprised two ferric carboxymaltose administrations, the cumulative dose of that initial course was analyzed as the exposure, with follow-up anchored to the first administration. Formulation, number of administrations, and cumulative elemental iron dose were abstracted. Later re-treatment beyond the initial course was not modeled as a separate time-dependent exposure.

Data collection and variable definitions

Data were abstracted from electronic medical records using a predefined chart-review dataset. Baseline variables included demographics, tumor type, body weight, current anticancer treatment status, chemotherapy category, documented bleeding source or suspected anemia cause, and key laboratory values obtained closest to the index date, including Hb, ferritin, serum iron, total iron-binding capacity, transferrin saturation (TSAT), C-reactive protein, albumin, and serum phosphate when available. Iron phenotype was classified as absolute iron deficiency (ferritin < 100 ng/mL and TSAT < 20%), functional iron deficiency (ferritin ≥ 100 ng/mL and TSAT < 20%), or non-iron-deficient/other when these criteria were not met. RBC transfusion was defined as any packed RBC administration documented after the index date; the date and number of units were recorded when available. Safety data were obtained from infusion records and follow-up notes. Serum phosphate analyses were restricted to available paired values and were descriptive.

Follow-up windows

Baseline was defined as the last pre-treatment assessment before the index date. Prespecified follow-up windows were 21–45 days after the index date for the 1-month window and 70–110 days for the 3-month window. For each window, the Hb value closest to the nominal target day (day 30 or day 90) was selected; if two values were equally close, the later value was used. Patients without an in-window Hb

measurement were considered non-evaluable for Hb-based analyses at that landmark. Reasons for 3-month non-evaluable status were categorized descriptively. No imputation was performed for missing Hb values.

Outcomes

The primary endpoint was Hb change from baseline to the 3-month window in patients with evaluable 3-month Hb and no RBC transfusion between the index date and the selected 3-month Hb assessment. This non-transfused landmark set was used to minimize confounding of Hb change by interim transfusion. Secondary endpoints were Hb change from baseline to 1 month, Hb change from 1 to 3 months among paired measurements, the 3-month Hb responder rate (increase ≥ 1.0 g/dL from baseline without interim RBC transfusion), Hb durability among 1-month responders, observed transfusion avoidance, follow-up completion/attrition, and safety outcomes. Observed transfusion avoidance was defined as absence of documented RBC transfusion after the index date within the specified window. Because complete post-transfer, post-death, or out-of-hospital follow-up information was not uniformly available, 3-month transfusion avoidance was analyzed descriptively as a window-based outcome rather than as a time-to-event endpoint; patients who died or transferred before day 110 were not assumed to be transfusion-free through the full window.

Statistical analysis

Analyses were descriptive and exploratory. Continuous variables were summarized as mean ± standard deviation or median [interquartile range], as appropriate; categorical variables were summarized as number (percentage). Within-patient Hb changes were analyzed using paired t-tests when paired differences were approximately normally distributed and Wilcoxon signed-rank tests otherwise. Responder and transfusion-avoidance proportions were summarized with exact 95% confidence intervals when appropriate. No imputation was performed. Patients who received RBC transfusion before the relevant Hb assessment were excluded from the corresponding Hb-change and responder analyses, and patients without in-window Hb values were excluded from Hb-based analyses for that window but retained in descriptive follow-up and transfusion summaries. All statistical analyses were performed using R (R Foundation for Statistical Computing, Vienna, Austria). All tests were two-sided, and $p < 0.05$ was considered statistically significant for the primary endpoint.

Ethics

This retrospective observational study was approved by the Institutional Review Board of University of Toyama (R2023041). The requirement for written informed consent was waived, and an opt-out approach was used in accordance with institutional policy and the Declaration of Helsinki.

Results

Cohort assembly and follow-up status

The cohort comprised 65 adults with active solid malignancy who received an initial course of high-dose intravenous iron monotherapy and had baseline hemoglobin (Hb) data. Figure 1 summarizes cohort assembly and follow-up through the prespecified landmark windows. In-window Hb measurements were available in 62/65 patients (95.4%) at 1 month and 42/65 (64.6%) at 3 months. Of the 62 patients with 1-month Hb data, 51 had no documented red blood cell (RBC) transfusion before the selected 1-month assessment and formed the non-transfused 1-month landmark set. At 3 months, 23 patients were non-evaluable for Hb because of transfer or community follow-up (n = 15), death (n = 7), or data cutoff/window not reached (n = 1). Of the 42 patients with 3-month Hb data, 27 had no documented RBC transfusion before the selected assessment and formed the prespecified primary non-transfused 3-month analysis set.

Baseline characteristics

Baseline characteristics and index iron exposure are shown in Table 1. Median age was 70 years (interquartile range [IQR] 63–77), and 24/65 patients (36.9%) were women. Upper gastrointestinal and pancreatobiliary tumors were the dominant tumor groups (21/65 each, 32.3%), and 45/65 patients (69.2%) were receiving chemotherapy at the index iron course. Mean baseline Hb was 8.31 ± 1.45 g/dL, median ferritin was 131.5 ng/mL (IQR 21.8–303.5), and median transferrin saturation was 11.6% (IQR 7.4–16.9). Functional iron deficiency was the most common classifiable iron phenotype (32/64, 50.0%), followed by absolute iron deficiency (25/64, 39.1%). Ferric carboxymaltose was used in 59/65 patients (90.8%), with ferric derisomaltose used in the remaining 6/65 (9.2%); the initial iron course was 500 mg in 38/65 (58.5%) and 1000 mg in 27/65 (41.5%).

Table 1
Baseline Characteristics and Index Intravenous Iron Treatment Exposure

Characteristic	Overall cohort (N = 65)
Demographics and clinical characteristics	
Age, years	70 [63–77]
Female sex	24/65 (36.9%)
Body weight, kg	53.7 [47.4–60.7]
Tumor group	
Upper gastrointestinal	21/65 (32.3%)
Pancreatobiliary	21/65 (32.3%)
Colorectal	11/65 (16.9%)
Sarcoma/mesenchymal	5/65 (7.7%)
Cancer of unknown primary	3/65 (4.6%)
Other	4/65 (6.2%)
Current treatment status at index	
On chemotherapy	45/65 (69.2%)
Treatment-naive / pre-treatment	9/65 (13.8%)
Best supportive care	9/65 (13.8%)
Radiotherapy	2/65 (3.1%)
Chemotherapy category	
Myelosuppressive	36/65 (55.4%)
Non-myelosuppressive	9/65 (13.8%)
No systemic therapy / best supportive care	20/65 (30.8%)
Documented bleeding event	8/65 (12.3%)
Index iron treatment exposure	
Ferric carboxymaltose	59/65 (90.8%)

Continuous variables are presented as mean ± standard deviation or median [interquartile range], as appropriate. Categorical variables are presented as n/N (%). Tumor grouping was created for descriptive presentation. Iron phenotype was classifiable in 64 patients because ferritin or transferrin saturation was unavailable in one patient. Absolute iron deficiency was defined as ferritin < 100 ng/mL and transferrin saturation < 20%; functional iron deficiency was defined as ferritin ≥ 100 ng/mL and transferrin saturation < 20%.

Characteristic	Overall cohort (N = 65)
Demographics and clinical characteristics	
Ferric derisomaltose	6/65 (9.2%)
Initial iron course 500 mg	38/65 (58.5%)
Initial iron course 1000 mg	27/65 (41.5%)
Administered dose, mg/kg	10.8 [8.9–18.4]
Ganzoni-estimated iron need, mg	978 [831–1101]
Baseline laboratory values	
Hemoglobin, g/dL	8.31 ± 1.45
Ferritin, ng/mL	131.5 [21.8–303.5] (n = 64)
Serum iron, µg/dL	27 [18–45]
Total iron-binding capacity, µg/dL	279 [218–340]
Transferrin saturation, %	11.6 [7.4–16.9]
C-reactive protein, mg/dL	1.43 [0.53–5.96]
Albumin, g/dL	3.1 [2.7–3.6]
Serum phosphate, mg/dL	3.35 [2.90–3.88] (n = 62)
Iron phenotype	
Absolute iron deficiency	25/64 (39.1%)
Functional iron deficiency	32/64 (50.0%)
Non-iron-deficient/other	7/64 (10.9%)

Continuous variables are presented as mean ± standard deviation or median [interquartile range], as appropriate. Categorical variables are presented as n/N (%). Tumor grouping was created for descriptive presentation. Iron phenotype was classifiable in 64 patients because ferritin or transferrin saturation was unavailable in one patient. Absolute iron deficiency was defined as ferritin < 100 ng/mL and transferrin saturation < 20%; functional iron deficiency was defined as ferritin ≥ 100 ng/mL and transferrin saturation < 20%.

Hemoglobin outcomes

In the non-transfused 1-month landmark set (n = 51), mean Hb increased from 8.61 ± 1.38 g/dL at baseline to 9.65 ± 1.71 g/dL at 1 month (mean change + 1.05 ± 1.46 g/dL; 95% confidence interval [CI] 0.64–1.46; p < 0.001). In the primary non-transfused 3-month analysis set (n = 27), mean Hb increased from 9.01 ± 1.47 g/dL at baseline to 11.09 ± 1.67 g/dL at 3 months (mean change + 2.08 ± 1.72 g/dL; 95% CI 1.40–2.76; p < 0.001), indicating a greater Hb increase at the 3-month landmark. In the same 27

patients with paired 1- and 3-month values, mean Hb showed a further increase from 10.56 ± 1.47 g/dL at 1 month to 11.09 ± 1.67 g/dL at 3 months (mean change + 0.52 ± 1.27 g/dL; 95% CI 0.02–1.03; p = 0.043). Figure 2 shows the within-patient Hb trajectories in the 1-month and 3-month landmark sets.

Responder analyses

At 1 month, 27/51 patients (52.9%; exact 95% CI 38.5%–67.1%) achieved an Hb increase of at least 1.0 g/dL in the non-transfused landmark set. At 3 months, 17/27 patients (63.0%; exact 95% CI 42.4%–80.6%) met the same responder definition in the primary analysis set. Among 19 patients who were 1-month responders and had paired non-transfused 3-month follow-up, 16 (84.2%; exact 95% CI 60.4%–96.6%) maintained an Hb increase of at least 1.0 g/dL from baseline at 3 months.

Transfusion-related outcomes

Transfusion-related outcomes are summarized in Table 2. Observed transfusion avoidance within 1 month was 53/65 patients (81.5%; exact 95% CI 70.0%–90.1%). Across the whole cohort, 47/65 patients (72.3%) had no documented RBC transfusion during available in-system follow-up within 3 months; this whole-cohort figure is descriptive because patients who died or transferred before day 110 were not assumed to be transfusion-free through the full window. Among the 42 patients with an in-window 3-month Hb measurement under institutional observation, 27 (64.3%; exact 95% CI 48.0%–78.4%) had no documented RBC transfusion through the 3-month assessment.

Table 2
Follow-up, Efficacy, Transfusion-Related, and Safety Outcomes

Outcome	Analysis population	Value
1-month in-window Hb available	Whole cohort (N = 65)	62/65 (95.4%)
3-month in-window Hb available	Whole cohort (N = 65)	42/65 (64.6%)
3-month non-evaluable due to transfer/community follow-up	Whole cohort (N = 65)	15/65 (23.1%)
3-month non-evaluable due to death	Whole cohort (N = 65)	7/65 (10.8%)
3-month window not reached by data cutoff	Whole cohort (N = 65)	1/65 (1.5%)
1-month efficacy		
Non-transfused 1-month landmark set	Patients with in-window 1-month Hb and no documented RBC transfusion before landmark	n = 51
Baseline Hb, g/dL	Same as above	8.61 ± 1.38
1-month Hb, g/dL	Same as above	9.65 ± 1.71
Change in Hb from baseline to 1 month, g/dL	Same as above	+ 1.05 ± 1.46; 95% CI 0.64–1.46; p < 0.001
1-month responder rate (Hb increase ≥ 1.0 g/dL)	Same as above	27/51 (52.9%; exact 95% CI 38.5%–67.1%)
Observed transfusion avoidance within 1 month	Whole cohort (N = 65)	53/65 (81.5%; exact 95% CI 70.0%–90.1%)
3-month efficacy		
Primary non-transfused 3-month landmark set	Patients with in-window 3-month Hb and no documented RBC transfusion before landmark	n = 27
Baseline Hb, g/dL	Same as above	9.01 ± 1.47
3-month Hb, g/dL	Same as above	11.09 ± 1.67

Hb-based efficacy analyses were landmark-based available-case analyses without imputation. Patients who received RBC transfusion before the corresponding landmark were excluded from Hb change and responder analyses for that landmark. The 1-month window was defined as 21–45 days and the 3-month window as 70–110 days after the index iron administration. Observed transfusion avoidance over 3 months was treated as a descriptive window-based outcome rather than a time-to-event endpoint; patients who died or transferred before day 110 were not assumed to be transfusion-free through the full window. CI, confidence interval; Hb, hemoglobin; RBC, red blood cell.

Outcome	Analysis population	Value
Change in Hb from baseline to 3 months, g/dL	Same as above	+ 2.08 ± 1.72; 95% CI 1.40–2.76; p < 0.001
Paired 1- to 3-month Hb change, g/dL	Patients with paired 1- and 3-month Hb and no documented RBC transfusion before 3-month landmark (n = 27)	+ 0.52 ± 1.27; 95% CI 0.02–1.03; p = 0.043
3-month responder rate (Hb increase ≥ 1.0 g/dL)	Primary non-transfused 3-month landmark set	17/27 (63.0%; exact 95% CI 42.4%–80.6%)
Hb durability among 1-month responders	1-month responders with paired non-transfused 3-month follow-up (n = 19)	16/19 (84.2%; exact 95% CI 60.4%–96.6%)
No documented RBC transfusion through 3 months	Patients with full in-system 3-month follow-up (n = 42)	27/42 (64.3%; exact 95% CI 48.0%–78.4%)
No documented RBC transfusion during available in-system follow-up within 3 months	Whole cohort (N = 65); descriptive	47/65 (72.3%)
Safety		
Infusion reactions	Whole cohort (N = 65)	0
Clinically documented symptomatic hypophosphatemia	Whole cohort (N = 65)	0
Paired serum phosphate available	Whole cohort (N = 65)	54/65 (83.1%)
Baseline serum phosphate, mg/dL	Patients with paired phosphate values (n = 54)	3.40 [2.93–3.78]
Post-treatment serum phosphate, mg/dL	Patients with paired phosphate values (n = 54)	3.30 [2.75–3.80]
Mean change in serum phosphate, mg/dL	Patients with paired phosphate values (n = 54)	−0.20 ± 1.06; p = 0.181
Post-treatment phosphate < 2.0 mg/dL	Patients with post-treatment phosphate measured (n = 54)	7/54 (13.0%)
Post-treatment phosphate ≤ 1.0 mg/dL	Patients with post-treatment phosphate measured (n = 54)	1/54 (1.9%)

Hb-based efficacy analyses were landmark-based available-case analyses without imputation. Patients who received RBC transfusion before the corresponding landmark were excluded from Hb change and responder analyses for that landmark. The 1-month window was defined as 21–45 days and the 3-month window as 70–110 days after the index iron administration. Observed transfusion avoidance over 3 months was treated as a descriptive window-based outcome rather than a time-to-event endpoint; patients who died or transferred before day 110 were not assumed to be transfusion-free through the full window. CI, confidence interval; Hb, hemoglobin; RBC, red blood cell.

Outcome	Analysis population	Value
Other clinically recorded iron-related adverse events	Whole cohort (N = 65)	0

Hb-based efficacy analyses were landmark-based available-case analyses without imputation. Patients who received RBC transfusion before the corresponding landmark were excluded from Hb change and responder analyses for that landmark. The 1-month window was defined as 21–45 days and the 3-month window as 70–110 days after the index iron administration. Observed transfusion avoidance over 3 months was treated as a descriptive window-based outcome rather than a time-to-event endpoint; patients who died or transferred before day 110 were not assumed to be transfusion-free through the full window. CI, confidence interval; Hb, hemoglobin; RBC, red blood cell.

Safety outcomes

No infusion reactions or clinically documented symptomatic hypophosphatemia were identified in routine records. Paired serum phosphate values were available in 54 patients. Median phosphate changed from 3.40 mg/dL (IQR 2.93–3.78) at baseline to 3.30 mg/dL (IQR 2.75–3.80) after treatment; the mean change was − 0.20 ± 1.06 mg/dL (p = 0.181). Post-treatment phosphate was < 2.0 mg/dL in 7/54 tested patients (13.0%) and ≤ 1.0 mg/dL in 1/54 (1.9%), with no documented symptomatic cases. Other clinically recorded iron-related adverse events were not identified (Table 2).

Discussion

In this updated real-world cohort from an ESA-free Japanese oncology setting, high-dose intravenous iron monotherapy was associated with Hb improvement at 3 months among evaluable non-transfused patients. The Hb increase appeared to deepen from 1 to 3 months in the paired non-transfused population, and observed transfusion avoidance was descriptively high during available follow-up. These findings suggest a clinically recognizable short-to-intermediate hematologic signal in selected patients treated with ferric carboxymaltose or ferric derisomaltose during routine solid-tumor care. At the same time, substantial attrition by the 3-month landmark requires cautious interpretation. The results should therefore be read as outcomes in an evaluable non-transfused landmark set, not as evidence that all treated patients would experience the same course.

This study extends, rather than duplicates, our prior 1-month report from the same ESA-free practice environment, which described an early Hb rise, observed transfusion avoidance, and short-term safety after high-dose intravenous iron monotherapy[7]. The present analysis adds an updated cohort, a prespecified 3-month landmark, and paired 1- to 3-month observation in non-transfused patients. This longer window is clinically relevant because Hb recovery after iron repletion may continue beyond the first post-treatment month, whereas transfusion needs and follow-up continuity become clearer over short-to-intermediate oncology care. The direction of the findings is also consistent with evidence that intravenous iron without ESA support can improve Hb outcomes in cancer-associated anemia[4–6]. Nevertheless, the present data remain observational and landmark-based, and the apparent deepening of response should be interpreted as hypothesis-generating rather than a generalizable treatment effect.

For IJCO readers, the main clinical implication is practical anemia management in settings where ESAs are not used for chemotherapy-induced anemia. In such settings, intravenous iron and RBC transfusion are the principal supportive-care options. High-dose intravenous iron may be a pragmatic option for selected patients when iron-restricted erythropoiesis is suspected or present, particularly because ferric carboxymaltose and ferric derisomaltose can deliver substantial iron repletion in one or a few visits. The observed transfusion-avoidance findings are clinically relevant because RBC transfusion entails visit burden, monitoring, and blood-resource use; however, they should be interpreted descriptively because this study had no concurrent comparator and did not evaluate symptoms, quality of life, treatment continuation, or patient preferences. Palliative-care literature also emphasizes careful selection and timing of transfusion in advanced cancer, reinforcing the need for individualized interpretation rather than routine substitution of one strategy for another[9], [10]. Thus, these data support the clinical relevance of evaluating high-dose intravenous iron as a supportive-care option in selected patients, but they do not establish that transfusion can be replaced.

Attrition should be interpreted both as a limitation and as a feature of real-world advanced-cancer care. Non-evaluable 3-month follow-up often reflected death, transfer to another institution, or community-based follow-up, which are clinically meaningful care trajectories rather than merely administrative losses. At the same time, attrition creates selection bias: the 3-month landmark results apply only to patients who remained alive, under follow-up, and non-transfused before the selected Hb assessment. Patients who became non-evaluable should not be assumed to have maintained Hb improvement or remained transfusion-free. Therefore, the 3-month findings describe outcomes in an evaluable landmark population, not the expected course of all patients who receive high-dose intravenous iron. This distinction is important when translating landmark data into clinical expectations for patients with unstable follow-up.

Our cohort complements, rather than replaces, prospective studies. Existing prospective ESA-free evidence has used scheduled shorter-term or protocolized follow-up, such as the 8-week phase II study of ferric carboxymaltose monotherapy by Jang et al.[5]. In addition, a multicenter prospective protocol in gastrointestinal cancer plans structured eligibility, protocolized ferric carboxymaltose dosing, and predefined Hb and quality-of-life assessments over 12 weeks[11]. Such designs are essential for validation because they can define eligibility, treatment timing, re-dosing, laboratory monitoring, and patient-centered endpoints more consistently than retrospective chart review. The present routine-care cohort adds a different perspective by showing how Hb outcomes, transfusion documentation, and follow-up incompleteness appear in everyday oncology practice, where patients may transition out of hospital-based monitoring before a 3-month landmark.

Several limitations should be emphasized. First, this was a retrospective single-center study with a modest sample size and no concurrent comparator; causal inference is therefore not possible. Second, 3-month attrition introduced selection bias, and the non-transfused landmark set was restricted to patients who were alive, followed, and not transfused before the landmark Hb assessment. Third, transfusion outcomes were descriptive because reliable censoring after death, transfer, or out-of-system

care was incomplete. Fourth, re-treatment beyond the initial iron course was not modeled as a time-dependent exposure. Fifth, safety assessment depended on routine documentation and available phosphate data, so absence of recorded events should not be equated with comprehensive safety confirmation. Finally, no direct patient-reported symptom or quality-of-life assessment was performed. Accordingly, these results should be regarded as exploratory real-world evidence that supports prospective validation of high-dose intravenous iron monotherapy in ESA-free oncology practice.

Conclusion

In an ESA-free Japanese oncology setting, high-dose intravenous iron monotherapy was associated with 3-month Hb improvement among evaluable non-transfused patients, with descriptively high observed transfusion avoidance. Substantial attrition contextualizes the landmark findings and limits generalizability. These exploratory real-world data support prospective validation in selected patients with cancer-related anemia.

Declarations

Competing interests

The authors have no relevant financial or non-financial interests to disclose.

Ethics Approval

The study was conducted in accordance with the Declaration of Helsinki, and approved by the Institutional Review Board of University of Toyama (approval ID R2023041; June 1, 2023).

Consent to participate

Patient consent was waived due to the retrospective design (opt-out procedure).

Consent to publish

Not applicable (no individual identifying data are included).

Generative AI use

During the preparation of this manuscript, the authors used ChatGPT (OpenAI) and Grammarly Pro as AI-assisted tools to improve language and readability. After using these tools, the authors reviewed and edited the content as needed and take full responsibility for the content of the published article.

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Authors’ contributions

SK and YI conceived the study. SK and YI curated data. SK, MM, IO, YS, YN, YU, IM, AT, and IY contributed to data acquisition and interpretation. SK performed the analyses and drafted the manuscript. AK and RH provided critical revisions. All authors read and approved the final manuscript.

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Data availability

De-identified data for this study are stored on secure institutional servers at Toyama University Hospital. Owing to institutional policies and privacy restrictions, the data are not publicly accessible. Requests to access additional de-identified data should be directed to the corresponding author. Data will be made available upon reasonable request, subject to a data-sharing agreement and approval from the Institutional Review Board of Toyama University.

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Figures

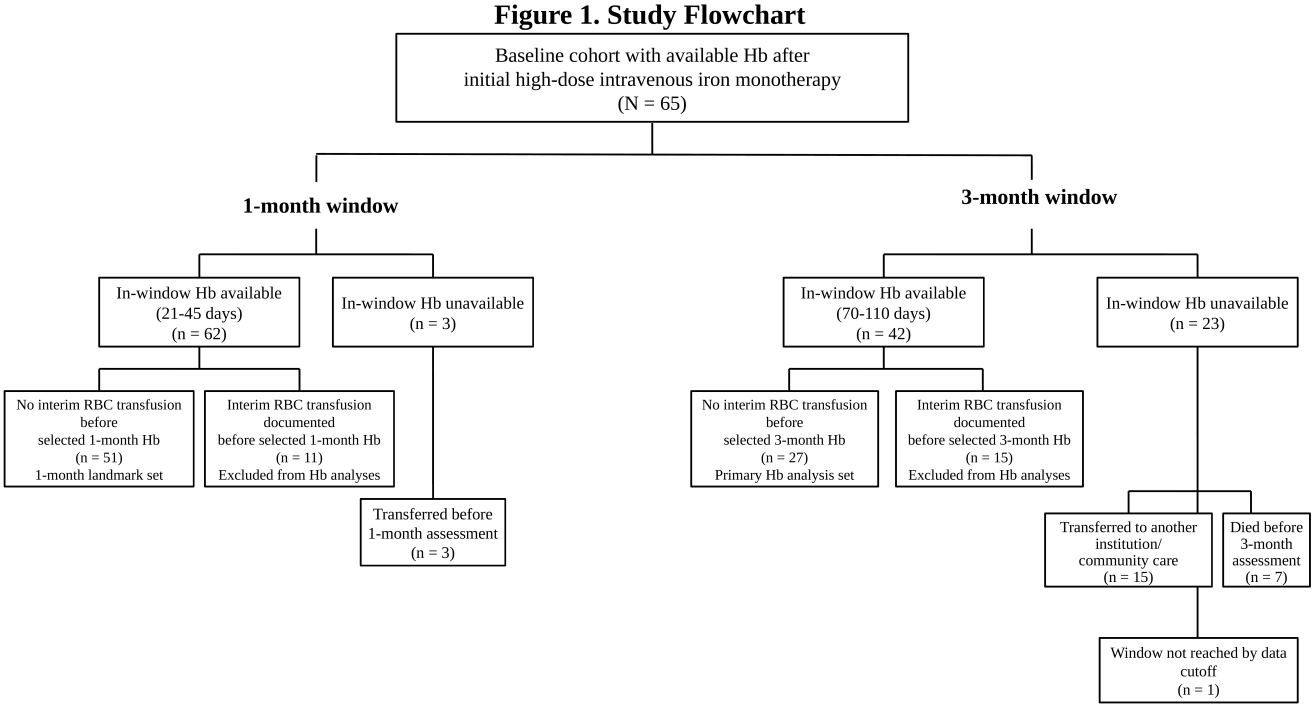
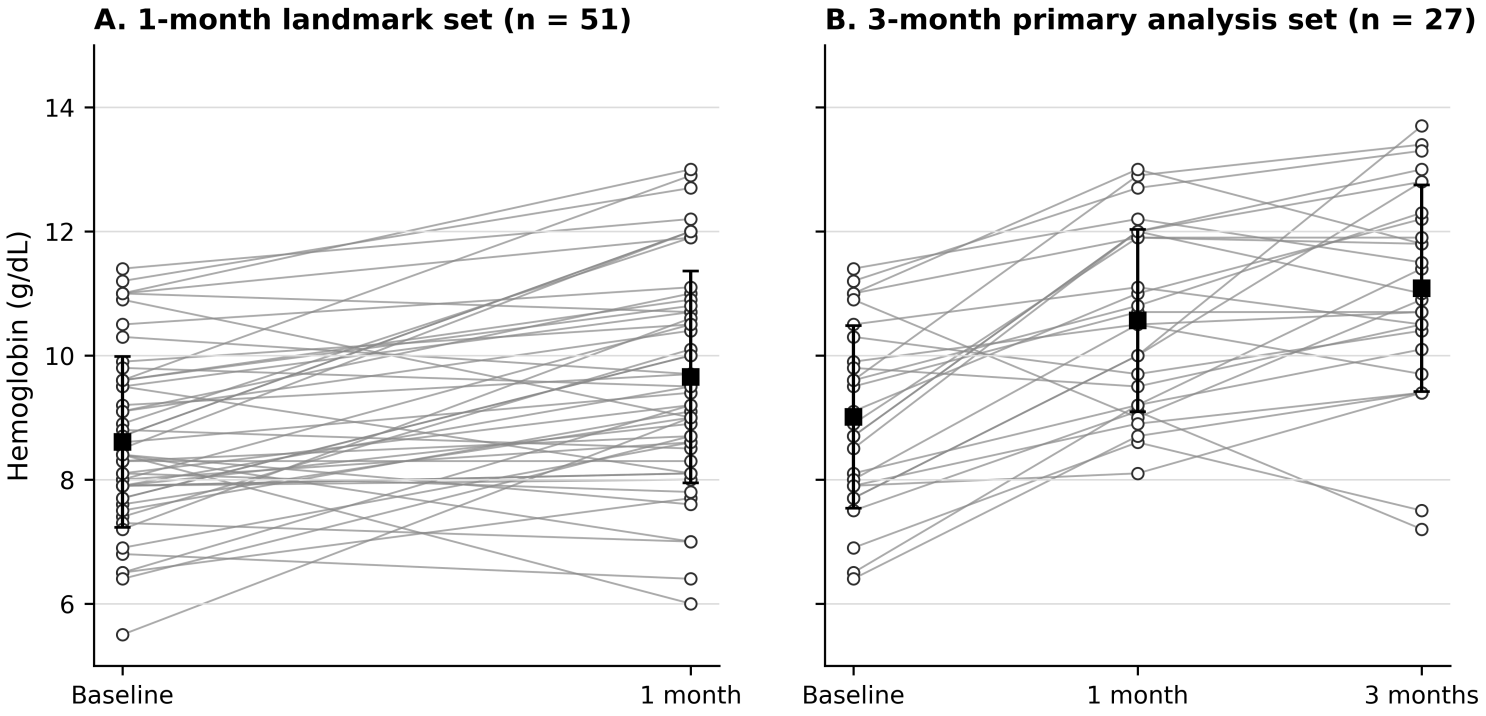


Figure 1

Study flowchart

The diagram summarizes cohort assembly from the baseline cohort (N = 65) to the prespecified 1-month (21–45 days) and 3-month (70–110 days) landmark windows. Patients with documented RBC transfusion before the corresponding landmark were excluded from Hb-based response analyses for that window but remained in descriptive summaries of follow-up and transfusion use. Hb, hemoglobin; RBC, red blood cell.



Open circles and thin lines indicate individual patients; black squares with error bars indicate mean ± SD.

Figure 2

Hemoglobin changes after high-dose intravenous iron monotherapy

(A) Hemoglobin (Hb) values at baseline and at 1 month in the non-transfused 1-month landmark set (n = 51). (B) Hemoglobin values at baseline, 1 month, and 3 months in patients with paired 1- and 3-month follow-up and no documented red blood cell (RBC) transfusion before the 3-month assessment (n = 27). Open circles and thin lines represent individual patients; black squares with error bars represent mean ± SD. The 1-month and 3-month landmark windows were defined as 21–45 days and 70–110 days, respectively, after the index iron administration. Hb, hemoglobin; RBC, red blood cell.