The Impact of Pre-Stem Cell Transplant Ferritin Level on Late Transplant Complications: An Analysis to Determine the Potential Role of Iron Overload on Late Transplant Outcomes

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Citation

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Abstract

Background: Iron overload has been associated with increased non-relapse mortality (NRM) in patients with acute myeloid leukemia (AML) and myelodysplastic syndrome (MDS) undergoing hematopoietic stem cell transplantation (HSCT). Elevated ferritin level pre-HSCT has been used as a marker for iron overload. It is unclear whether the negative effect of iron overload as measured by elevated ferritin level extends beyond the first three months post HSCT, as this would suggest a potential role for active management of iron overload post HSCT. Patients: Sixty-three patients with AML and MDS who underwent an allogeneic HSCT from a sibling or unrelated donor between January to December 2006, had a pre-HSCT ferritin level and were alive and disease free 90 days post HSCT. Results: Median age was 51. Patients with the lowest pre-HSCT ferritin level (Q1) had a trend towards improved overall survival and progression free survival when compared to patients with higher level (Q2-Q4) (P=0.06, and 0.125). Cumulative incidence of NRM at 2 years was 20 and 30% respectively (P=0.4). Conclusion: Pre-HSCT ferritin level may still have an impact on HSCT events beyond 3 months post transplant, suggesting a role for research into active management of iron overload with either phlebotomy or chelation.

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INTRODUCTION

The deleterious effects of iron overload on hematopoietic stem cell transplant (HSCT) outcomes in patients with thalassemia has been well documented [1, 2]. The role of iron overload in the setting of HSCT for non-thalassemia patients is less clear. Recent retrospective analysis have demonstrated that elevated pre-transplant serum ferritin is associated with an increase rate of non relapse mortality (NRM) in the first 100 days post HSCT in patients with hematologic malignancies [3-12] . The increase in NRM has been related to increases in rates of acute graft-versus-host-disease (GVHD), infections, and veno-occlusive disease (VOD). The underlying hypothesis relating an increase pre-transplant ferritin level to increase NRM rate is a presumed deleterious effect of iron deposition in vital organs that predispose to higher rates of infectious and non infectious complications [13-15].

Although phlebotomy is the treatment of choice for iron overload, transplant patients are generally anemic and are poor candidates for phlebotomy [16-18]. Iron chelation therapy with either deferoxamine or deferasirox can be considered, but rarely used in the peri-transplant period.[17] Deferoxamine requires either intravenous or subcutaneous administration and deferasirox is associated with increased creatinine levels (11-38%), fever (19%), abdominal pain (8-14%), and skin rash (8-11%) which overlap with commonly seen side effects post allogeneic transplant, limiting the use of these agents particularly during the early post transplant period (first 90 days)[17-19].

Moderate to severe iron overload at the time of transplant has been shown to persist for several years in both thalassemic and non-thalassemic patients [20, 21]. However, the impact of this condition on late transplant outcomes is uncertain. Outside of thalassemic patients, treatment has been primarily focused on patients with clinical evidence of liver dysfunction [22-24].

Although the evidence suggests a correlation between iron overload and the development of post transplant complications, the transplant physician can do little to change this issue during the early post transplant period. However, at three months post HSCT, most patients will have recovered hemoglobin values to a level appropriate for phlebotomy, and will be more likely to tolerate systemic iron chelation therapy. We performed a retrospective single institutional study to determine the impact of pre-stem cell transplant ferritin level on late transplant complications in patients with acute myeloid leukemia (AML) and high risk myelodysplastic syndrome (MDS) undergoing HSCT and surviving at least 90 days without relapse. We hypothesized that patients with the highest ferritin level pre-HSCT would have higher post transplant complications beyond three months. This would justify a prospective evaluation of the role of phlebotomy or systemic iron chelation therapy in these patients.

PATIENTS AND METHODS

ELIGIBILITY CRITERIA

Patients were eligible if they had a diagnosis of AML or high risk MDS, had undergone an allogeneic HSCT using peripheral blood or bone marrow progenitor cells from a matched sibling or unrelated donor during the year 2006 at the University of Texas MD Anderson Cancer Center (MDACC), had a pre-HSCT ferritin level within the 3 months preceding transplant, and were alive and disease free at 90 days post HSCT.

TRANSPLANT PROCEDURES AND SUPPORTIVE CARE

All patients and donors were treated on active protocols or standard of care guidelines available at MDACC at the time. Donor bone marrow or granulocyte colony stimulating factor (G-CSF) primed peripheral blood progenitor cells were procured using standard mobilization protocols and apheresis techniques. A minimum of 1×10^6 CD34+ cells per kilogram recipient was requested for stem cell transplant. Unrelated donor cells were obtained through the National Marrow Donor Program according to applicable guidelines. All patients signed written informed consent as required by our institution and the National Marrow Donor Program. This retrospective study was reviewed and approved by the institutional review board at MDACC.

Patients received either reduced intensity conditioning regimen consisting of fludarabine (30mg/m^2/day for 4 days) plus melphalan (140mg/m^2 once); fludarabine (40mg/m^2/day for 4 days) plus cyclophosphamide (50mg/kg once) plus TBI (200cGy) or an ablative conditioning with intravenous busulfan (130mg/m^2/day for 4 days) plus fludarabine (40mg/m^2/day for 4 days) as previously published [25-28]. All patients receiving unrelated donor progenitor cells received antithymocyte globulin (4 mg/kg over 3 days). GVHD prophylaxis was tacrolimus plus methotrexate as previously described [29]. Patients received standard supportive care including infection prophylaxis, transfusion support and growth factor administration according to institutional guidelines.

DEFINITIONS

The ferritin level was measured within the three months preceding HSCT. The assay used is a standard commercially available immunoassay, with normal values for our lab of 10 to 291 ng/ml. Ferritin level was classified into quartiles (Q). Quartiles were defined by sorting all patients' ferritin levels from high to low and separating the data into 4 groups or quartiles. The cutoff number for the lowest quartile was 1023: Q1- ferritin ≤ 1023 ng/ml; Q2- ferritin 1024-1566; Q3- ferritin 1567-2660; and Q4- ferritin > 2660.

Complete response (CR) prior to HSCT was defined as a normocellular bone marrow with less than 5% blast, evidence of normal maturation of marrow elements, absence of peripheral blood blast and platelet count greater than 100 x 10^9/L. Patients not in CR were categorized as “Other” (not responsive or untreated).

AML and MDS cytogenetic abnormalities were grouped according to published criteria [30, 31]. High risk MDS was MDS resulting from prior use of chemotherapy (secondary MDS), MDS unresponsive to conventional treatment, or MDS with poor-risk cytogenetics. Acute and chronic GVHD were scored using published guidelines [32, 33]. Patients were also classified according to a recently proposed prognostic score by Armand et al.[34].

STATISTICAL METHODS AND ENDPOINTS

The primary endpoints were overall survival (OS) and NRM. Secondary endpoints were relapse, progression free survival

(PFS) and incidence of chronic GVHD. All outcomes were evaluated starting on day 90 post allogeneic stem cell infusion. OS was estimated starting on day 90 until death from any cause with censoring performed at the date of last contact. PFS was determined from day 90 post transplant to day of documented relapse. NRM was death from any cause other than relapse. GVHD occurring anytime after day 90 post transplant was termed chronic GVHD. The incidence of NRM was estimated using the cumulative incidence method considering death in the presence of disease as a competing risk. The impact of pre-HSCT ferritin level on outcomes was evaluated in univariate analysis using the Cox proportional hazards model [35]. Statistical significance was determined at the 0.05 level, and it was two-sided. Analysis was performed using STATA (StataCorp.2001; Stata Statistical Software: Release 7.0.College Station, TX: Stata Corporation).

RESULTS

PATIENT AND DISEASE CHARACTERISTICS

Figure 1

Table I: Patients Baseline Characteristics

	Q1- pre-HSCT Ferritin ≤ 1023 590(25-1023)	Q2-Q4 pre-HSCT Ferritin >1023 1927 (1024 -15519)	P value
N	16 (%)	47 (%)	
Median Age	49 (22-70)	53 (21-68)	0.5
Sex – F/M	6 / 10 (38 / 62)	18 / 29 (38 / 62)	0.9
Disease Type			
Primary AML/MDS	13 (81)	37 (79)	0.6
Secondary AML/MDS	3 (19)	10 (21)	
Allotype			
Matched Siblings	11 (69)	20 (43)	0.07
MUD	5 (31)	27 (57)	
Cell Type			
BM	2 (12)	18 (38)	0.05
PBSC	14 (88)	29 (62)	
Cytogenetics			
Good	4 (25)	4 (8.5)	0.3
Intermediate	7 (44)	23 (49)	
Poor	5 (31)	20 (42.5)	
Armand Prognostic Score[34]			
1-3	14 (87)	28 (60)	0.04
>3	2 (13)	19 (40)	
Regimen Intensity			
Ablative	9 (56)	21 (45)	0.4
Reduced	7 (44)	26 (55)	
Status at SCT			
Remission	10 (62)	27 (57)	0.7
Other	6 (38)	20 (43)	

Q1: first quartile; HSCT: hematopoietic stem cell transplant; Q2-Q4: second to fourth quartiles; N: number; F: female; M: male; AML: acute myeloid leukemia; MDS: myelodysplastic syndrome; MUD matched unrelated donor; BM: bone marrow; PBSC peripheral blood stem cells.

Between January and December 2006, 105 patients with AML and high risk MDS underwent allogeneic HSCT. Ninety (85%) patients were alive and without relapse by day 90. Complete data, including pre-transplant ferritin level within the 3 months preceding transplantation was available for 76 (72%) patients. Thirteen patients who had cord transplant or mismatch related or unrelated transplant were excluded. We therefore evaluated 63 (60%) patients. Sixteen patients had pre-transplant ferritin level less than or equal to 1023 ng/ml (Q1), 16 patients each had levels between 1024-1566 ng/ml (Q2) and 16 had levels between 1567-2660 ng/ml (Q3), and 15 had ferritin level above 2660 ng/ml (Q4). Patients in Q1 (n=16) were compared to patients in Q2-4 (n=47) combined. Their baseline characteristics are summarized in Table I. Patients in Q1 had a lower likelihood

of having a high Armand Prognostic Score than those in Q2-Q4 [34]. There were no statistical differences between patients in Q1 and Q2-4 in terms of age, sex, primary or secondary AML and MDS, cytogenetics, regimen intensity, or remission status at transplant. Forty-three percent and 19% of patients in Q1 were in first CR (CR1) and second or third CR (CR2/CR3) respectively, compared to 32 and 23% in Q2-Q4 (P=0.7). Though not statistically significant, more patients in Q1 had matched related transplant and peripheral blood stem cell source (PBSC) as compared to patients in Q2-4.

Ferritin levels in pre and post transplant patients:

As shown in Figure 1a, there was a significant difference between the pre-transplant ferritin levels in Q1 and Q2-4 groups based on t-test analysis.

Figure 1b: There were significant increases in post transplant ferritin levels in both Q1 and Q2-Q4. Not all patients in Quartile patients had post-transplant ferritin tests. Therefore, only 10 patients in Quartile 1 and 37 patients in Quartiles 2-4 were analyzed. Nevertheless, t-tests analysis demonstrated that the pre and post differences in ferritin values were significant.

Figure 2

Figures 1a: The mean of pre-transplant ferritin levels in Quartile 1 was 560 ng/ml and the mean pre-transplant levels in Q2-4 was 2573 ng/ml. An independent sample t-test indicated that the differences between the pre-transplantion ferritin levels of Quartile 1 and Quartiles 2-4 were significant (p <0.001).

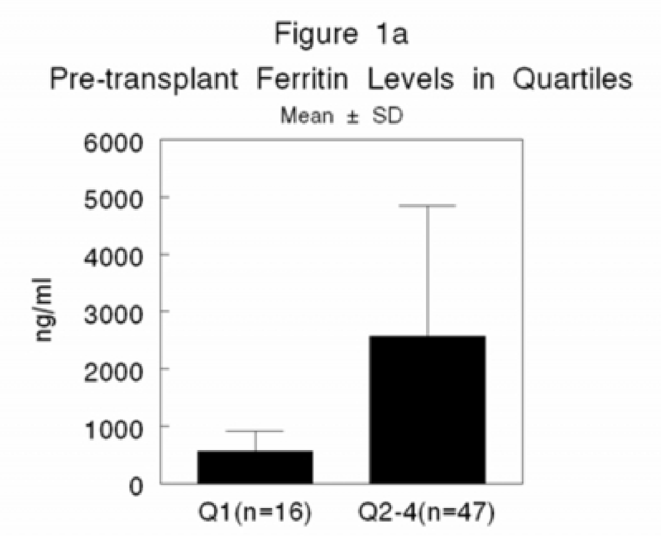
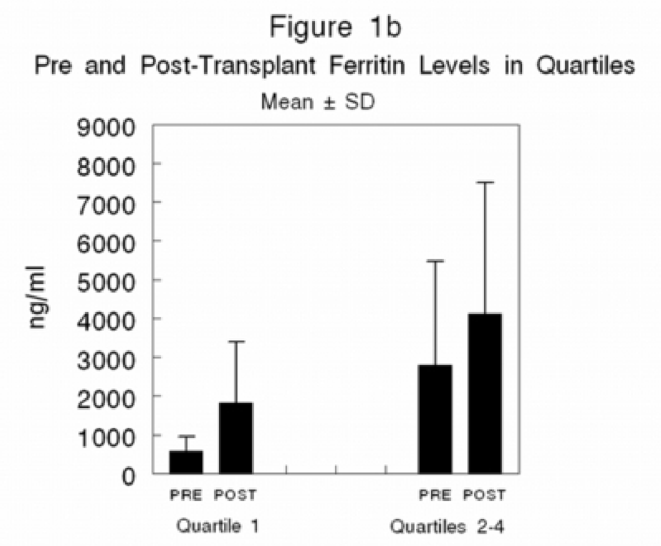


Figure 3

Figure 1b: For Quartile 1, the mean pre-transplant ferritin level was 590 and the mean post transplant ferritin levels was 1817 ng/ml (paired t-test p= < 0.04). For Quartiles 2-4, the mean pre-transplant level was 2799 ng/ml and mean post transplant was 4131ng/ml (paired t-test p= < 0.02). Therefore, the differences were significant based on t-test analysis.



IMPACT OF SERUM FERRITIN LEVEL ON OVERALL SURVIVAL AND PROGRESSION FREE SURVIVAL

Median follow-up in survivors from HSCT for patients in Q1 was 28 months (range 21–31) and 26 months (range 18-31) for patients in Q2-4. At the time of analysis, 4 patients (25%) in Q1 and 21 patients (45%) in Q2-4 had died. The median OS was not reached for patients in Q1 and it was 28 months for those in Q2-4. Though not statistically significant, there was a trend towards superior OS in patients with lower ferritin level pre transplant (Figure 1a). Actuarial OS was 94% versus 64% (hazard ratio (HR) 0.15, CI 0.2-1.1, P=0.06) for patients in Q1 and Q2-4 at 1 year and 75% versus 55% (HR 0.43, CI 0.1-1.3, P=0.13) at 2 years respectively. There was also a trend towards improved PFS for patients in Q1 as compared to those in Q2-4 (Figure 1b). Thirteen patients (81%) in Q1 versus 28 (60%) in Q2-4 were alive and disease free at 1 year (HR 0.4, CI 0.1-1.3, P=0.125) and 11 (69%) versus 23 (49%) were alive and disease free at 2 years (HR 0.5, CI 0.2-1.2, P=0.1). Patients with Armand Prognostic Score of < 3 had significantly better outcomes than those with scores of greater than 3. One and two year survival rates were 83 and 75% for patients with scores of 3 or less versus 48 and 33% for patients with higher scores respectively (p=0.006).

Figure 4

Figure 2: Overall Survival (a) and Progression Free Survival (b) according to pre-stem cell transplant ferritin level.

Figure 2a

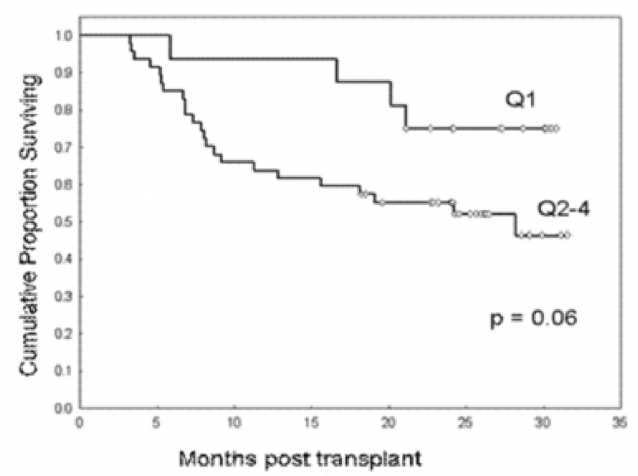
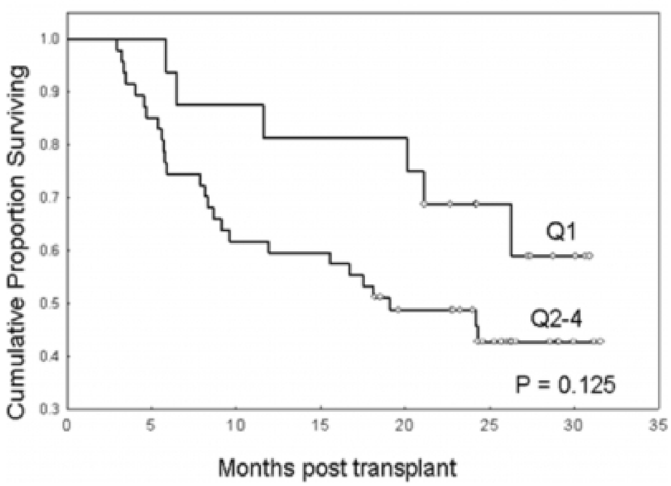


Figure 2b



IMPACT OF SERUM FERRITIN LEVEL ON RELAPSE, NON-RELAPSE MORTALITY AND CHRONIC GVHD

Figure 5

Table II: Relapse, Organ Function and Causes of Death According to Pre- Ferritin Level.

	Q1	Q2-Q4	P value
N	16	47	
Median follow-up in survivors, months (range)	28 (21-31)	26 (18-31)	NS
Relapse post transplant, N (%)	3 (19)	13 (28)	NS
Time to relapse, median days (range)	353 (196-799)	179 (90-739)	
cGVHD	12 (75)	15 (32)	0.02
Cause of death	4 (25)	21 (45)	
Relapse	1	10	
Infection	2	9	
GVHD	0	1	
Other	1	1	
Cumulative incidence NRM at 1 yr	6.3%	21%	NS
Cumulative incidence NRM at 2 yrs	20%	30%	NS
Median Hb (gm/dl) level at 3 months post HSCT (range)	11.8 (9-12.9)	11.1 (9.2-13)	NS
Peak AST- median (range)	45 (23-141)	43 (17-1769)	NS
Peak Bilirubin – median (range)	0.85 (0.4-1.2)	0.9 (0.3-14.8)	NS
Post HSCT F – median (range)	1382(108-5316)	2971(964-1537)	

N: number; Q1: first quartile; HSCT: hematopoietic stem cell transplant; Q2-Q4: second to fourth quartiles; cGVHD: chronic graft versus host disease; NRM: non relapse mortality; Hb: hemoglobin; AST: aspartate aminotransferase

At two years, 3 patients (19%) in Q1 and 13 patients (28%) in Q2-4 had relapsed (P = 0.3). Relapse was the number one cause of death in patients with a high ferritin level (Table II). The risk of death due to infection (12% in Q1 and 19% in Q2-4) was similar between the two groups. The cumulative incidence of NRM at 1 year was 6.3% versus 21% (HR 0.3, CI 0.03-2.2, P=0.2), and 20% versus 30% at 2 years (HR 0.5, CI 0.2-1.9, P=0.4) for patients in Q1 and Q2-4 respectively. Seventy-five percent of patients in Q1 had chronic GVHD as compared to 32% in Q2-4 (P=0.02). This was likely due to more patients in Q1 having received peripheral blood stem cells as their graft source [36, 37].

DISCUSSION

Figure 6

Table III: Impact of Pre-Stem Cell Transplant Ferritin Level on Transplant Outcome: Summary of Largest Series Published to Date.

Reference #	N	Disease	Ferritin Cut-off	Conclusion
3	190	Heme Malignancies	>1000 ng/ml	Increased NRM due to infection and organ failure
4	922	Heme Malignancies	>2515 ng/ml	Increased NRM in AML and MDS patients
9	253	Heme Malignancies	>1910 ng/ml	Increased NRM due to infection and non pulmonary organ failure
11	357	MDS	>1000 ng/ml	Increased NRM independent of transfusion dependency.
12	172	MDS	>1000 ng/ml	No increased in NRM

Previous studies have shown that elevated pre-transplant ferritin level correlates with increase iron overload and is an independent risk factor for NRM and OS post HSCT in patients with hematologic malignancies [3-11]. The largest of these studies are summarized in Table III. Most demonstrate that pre-HSCT ferritin level of ≥1000 ng/ml is associated with a significant increase in NRM primarily due to infectious and non infectious complications. Although ferritin is impacted by multiple factors, these studies suggested that the negative effect of increased serum ferritin level is related to increases in total body iron content and abnormal iron deposition in tissues (particularly liver and heart).

Studies on the prevention of iron overload in patients with hematologic malignancies are on-going. The efficacy of these interventions is still uncertain. It is therefore likely that many patients proceeding to HSCT will have abnormal iron deposition in tissues, as reflected by elevated pre-HSCT ferritin level. Aggressive iron management in the peri-transplant period is difficult since the most commonly used therapeutic strategies for iron overload are difficult to apply. Hemoglobin levels are generally less than 10 gm/dl during the first 3 months post HSCT, making phlebotomy impractical. The potential for severe gastrointestinal or renal toxicities in the context of oral or intravenous iron chelating agents make these agents difficult to use during the first three months post HSCT. However, if the effects of elevated pre-HSCT ferritin level can still be seen in patients surviving at least 3 months post transplant, it would be worthwhile to study the effects of phlebotomy and/or iron chelation therapy in these patients.

The results of this study show that serum ferritin level continues to increase in most patients during the peri-transplant period, probably due to inflammation and continued iron tissue deposition from transfused red blood cells. We measured post transplant ferritin levels at least 3 months post HSCT. However, it has been shown that moderate to severe iron overload in thalassemia patients at the time of transplant still persist for several years post transplant, with a significant proportion of NRM occurring even after 3 months post HSCT[20]. This likely holds true for all patients with hematologic malignancy, undergoing HSCT. Of particular interest in this study is that even three months post HSCT, patients who had higher pre-HSCT ferritin levels tended to do worse.

Although chronic GVHD was higher in patients in Q1, due to the fact that a higher number of patients in Q1 had PBSC (88% vs. 62% in Q2-4; P= 0.05), studies have shown that the higher percentage of cGVHD in related donor transplant using PBSC does not translate to a statistical difference in PFS or OS[36, 37]; and although more patients in Q1 had transplant from a matched related donor than those in Q2-4 (P=0.07), equivalent survival has been shown for sibling and unrelated allogeneic HSCT[38], excluding these two factors as confounders.

The limitations of this study are obvious. The retrospective nature and the small number of patients do not allow strong conclusions regarding the role of elevated ferritin level and late transplant events. Notwithstanding, these data should encourage further retrospective analysis and facilitate the design and implementation of prospective trials looking at the role of aggressive iron management in patients with elevated ferritin level three months post HSCT. Of particular importance for such studies are the following observations derived from this analysis: a) Substantial proportions of patients have ferritin level greater than 1000 ng/ml at three months post HSCT without any obvious untoward effects; b) The pre-HSCT Armand prognostic score is still relevant in patients alive and in remission three months post HSCT; c) Only 50% of patients would be candidates for phlebotomy three months post HSCT. Hence phlebotomy and iron chelation therapy need to be explored in this setting. The role of erythroid stimulating factors to increase feasibility of phlebotomy in this setting needs to be explored; and d) Given that significant infectious and non-infectious complications can still occur beyond three months post HSCT, the impact of aggressive iron management on these complications needs to be explored.

In conclusion, we have demonstrated that the negative impact of elevated pre-transplant ferritin level may persist longer than three months post transplant. Hence the potential role for tissue iron removal either by phlebotomy or chelation, and the impact on post transplant survival and late transplant complications needs to be prospectively studied. Better measures of tissue iron content such as Magnetic Resonance Imaging, Superconducting Quantum Interference Devices, and composite scores should also be incorporated into these studies [21, 39-42].

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