Intravenous Iron in the Perioperative Setting

To the Editor: In an attempt to provide a short term, practical, and effective regimen for perioperative anemia therapy as an alternative to autologous blood transfusion, Rutherford et al., evaluated three different regimens of recombinant human erythropoietin and concluded that irrespective of dose, "normal" iron stores for basal erythropoiesis may not always be sufficient to supply optimal amounts of iron for the accelerated erythropoiesis associated with acute recombinant erythropoietin administration, even with oral iron supplementation [1]. The comorbidity burden of surgical complications of perioperative anemia, present in one-third to one-half of all surgical patients remains clinically and economically formidable.

Perioperative allogeneic blood transfusion is associated with an increased postoperative infection rate, longer hospital stays, poorer outcomes, and increased cost. Much of the data on the use of erythropoietic therapy in the perioperative setting is observational. Garcia Erce et al., randomized patients undergoing elective knee arthroplasty who had preoperative hemoglobin levels of <13.0 g/dl to one dose of 40,000 units of erythropoietin plus two 200 mg doses of intravenous iron sucrose plus or minus red cell salvage. Both arms were compared to intrainstitutional historic controls. The observed transfusion reduction was nearly 90% with no significant difference in the two treatment arms [2]. In a prospective, randomized controlled study Serrano et al. studied 200 patients with hip fractures and hemoglobin levels <12 g/dl randomized to the standard no treatment of 600 mg of intravenous iron sucrose without erythropoiesis stimulating agents, preoperatively [3]. Perioperative transfusions overall were reduced from 41 to 33% and with subcapital fractures, more likely to be transfused, from 46 to 14% with intravenous iron. No quantitatively significant toxicity was observed with intravenous iron in either study.

Despite such a formidable benefit, regulatory bodies do not recommend the routine use of intravenous iron in anemic subjects undergoing elective surgery. Shander et al. described a multidisciplinary, multimodal, individualized strategy collectively termed Patient Blood Management with the aim to reduce allogeneic blood transfusion [4]. Perioperative anemia is detected and treated along with a higher transfusion threshold if or when transfusion is indicated. In an amalgam of published evidence (see Fig. 1, presented by Shander at the 2014 Annual Meeting of the European Society of Anaesthesiology) the use of allogeneic red blood cell transfusion provides the lowest benefit, highest risk, and sadly, has the highest use The Spanish consensus statement recommends routine, proactive diagnostic, and interventional anemia management [5].

In line with these conclusions, the clinical practice guidelines published by the American Association of Blood Banks [6] recommend adhering to a restrictive transfusion strategy (7–8 g/dl) in hospitalized stable patients as well as those with preexisting cardiovascular disease and limit transfusion to those with symptoms.

In a pooled analysis of 2,547 perioperative patients who underwent either hip fracture repair or lower limb arthroplasty, Munoz et al. reported a decrement in transfusion rate from 48.8 to 32.4% in those who received perioperative intravenous iron versus those who did not [7]. Postoperative infections were reduced from 26.9 to 10.7%, length of stay from 13.4 to 11.9 days and remarkably thirty day mortality from 9.4 to 4.8% in the IV iron group.

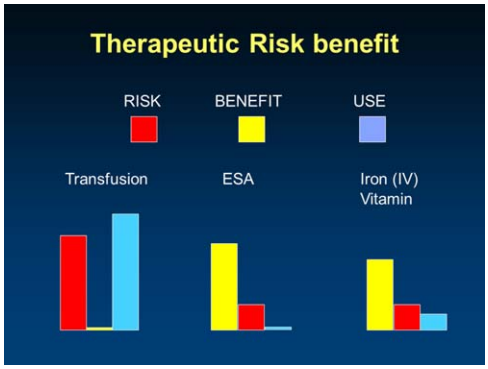

Figure 1. Therapeutic risk benefit and use analysis for red cell transfusion, ESA, and IV iron/vitamin supplementation. Kindly provided by Aryeh Shander, Chief, Anesthesiology, Englewood Medical Center and presented at the 2014 Annual Meeting of the European Society of Anaesthesiology. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

Nonetheless, perioperative anemia management is not a priority for most surgeons. A simple therapeutic paradigm directing the administration of intravenous iron 2–4 weeks preoperatively would now be nearly seamless with the availability of four new intravenous iron whose carbohydrate cores bind the elemental iron much more tightly, allowing full replacement dosing in a single 15–60 min visit. The cost/benefit would be substantial. In my community, the actual Committee for Medicare and Medicaid Services payment for two units of blood, administered in the ambulatory setting is greater than $5,200 based on Explanation of Benefit receipts mailed to patients. In contradistinction, the administration of a complete replacement dose of intravenous iron ranges from $290–$1,000 and avoids all of the morbidity of allogeneic blood transfusion. While this therapy has been proven to be safe and effective it remains underutilized. At a time when resources are scarce the adoption of intravenous iron as a standard for preoperative anemia is likely to be clinically and economically important as well as prognosis changing.

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References

1. Rutherford C, Schneider T, Dempsey H, et al. Efficacy of different dosing regimens for recombinant human erythropoietin in a simulated perisurgical setting: The importance of iron availability in optimizing response. Am J Med 1994;96:139–145.
2. Cuenca J, Garcia-Erce J, Martinex F, et al. Perioperative intravenous iron, with or without erythropoietin, plus restrictive transfusion protocol reduce the need for allogeneic blood after knee replacement surgery. Transfusion 2006;46:1112–1119.
3. Serrano J, Ugalde P, Cabello L, et al. Role of perioperative intravenous iron therapy in elderly hip fracture patients: A single-center randomized controlled trial. Transfusion 2011;51:97–104.
4. Shander A, Van Aken H, Colomina M, et al. Patient blood management in Europe. Br J Anaesth 2012;109:55–68.
5. Leal-Noval S, Munoz M, Asuero M, et al. Spanish consensus statement on alternatives to allogeneic blood transfusion: The 2013 update of the "Seville Document". Blood Transfus 2013;11:585–610.
6. Carson J, Grossman B, Kleinman S, et al. Red blood cell transfusion: A clinical practice guideline from the AABB. Ann Int Med 2012;157:49–58.
7. Munoz M, Gomez-Ramirez, Cuenca J, et al. Very-short-term perioperative intravenous iron administration and postoperative outcome in major orthopedic surgery: A pooled analysis of observational data from 2547 patients. Transfusion 2014;54:289–299.

Factors affecting outcome of allogeneic stem cell transplantation as salvage in patients with acute myeloid leukemia primary refractory to intensive induction therapy

To the Editor: We read with great interest the manuscript by Jabbour and colleagues entitled "Allogeneic stem cell transplantation (SCT) as initial salvage for patients with acute myeloid leukemia refractory to high-dose cytarabine-based induction chemotherapy" [1]. The authors reported that allogeneic SCT was associated with superior overall survival (OS) compared to salvage chemotherapy, with a 3-year OS rate of 39% in the SCT group. Moreover, in the 28 transplanted patients, they found that a higher percentage of bone marrow (BM) blasts at SCT was associated with inferior outcome and that relapse after transplant was the major cause of treatment failure.

We reviewed our database and identified 34 patients with AML primary refractory after intensive induction chemotherapy who underwent allogeneic SCT between 2000 and 2013. All patients received induction chemotherapy including high-dose (conventionally defined as $\geq$2 g/m^2/day) cytarabine (HDAC) and idarubicin (10 mg/m^2/day), associated in 31 cases with fludarabine ($n = 27$) or etoposide ($n = 4$). Twenty-seven patients received at least a second course with HDAC and idarubicin, without achieving complete remission (CR). Median number of chemotherapy courses before SCT was 2 (range, 1–4). Median age at SCT was 55 years (range, 27–69), and SCT was performed at a median of 5.5 months (range, 1.6–10) from diagnosis. Twenty-one patients (62%) received grafts from a sibling donor and 13 (38%) from a matched unrelated donor. In 27 patients (79%), stem cells source was peripheral blood (PB), while BM stem cells were used in seven cases. Patients were conditioned either with myeloablative ($n = 18$) or reduced-intensity conditioning ($n = 16$) regimens. OS was defined as time from SCT to death or last follow-up.

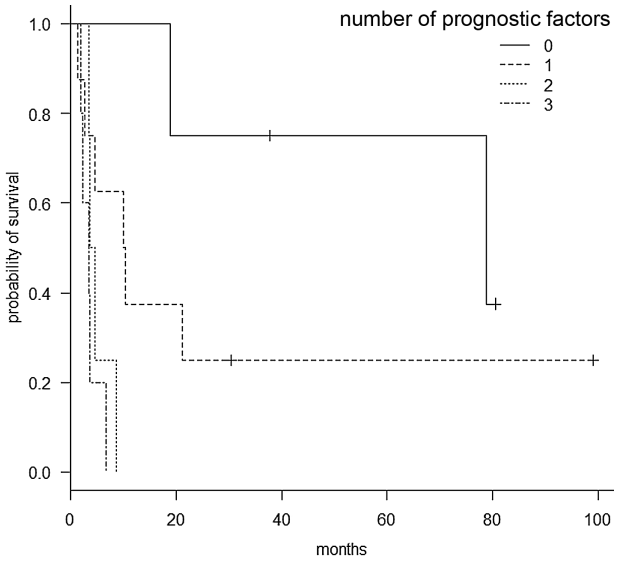

Figure 1. OS according to the number of adverse prognostic factors: WBC ≥10,000/ml, PLT ≤30,000/ml, and circulating blasts.

Thirty patients (88%) died, with a median OS of 4.5 months (95%CI 2.6–8.6) and a 3-year OS of 18% (95%CI 7–32). Cause of death was disease relapse/progression in 23 cases (77%), while the remaining 7 (23%) died of nonrelapse mortality (NRM). Twenty-nine patients were evaluable for response after SCT, as five died of early NRM. Nineteen patients (66%) achieved CR: 13/19 (68%) relapsed after a median of 3.4 months (range 1.7–18.2) and survived for a further 1.4 months (range 0.4–9); among the six patients in sustained CR, four are alive and two died of NRM after 79 and 55 months. Ten patients (34%) had resistant leukemia after SCT and died in a median of 2.5 months (range, 1.4–6.6).

Considering pretransplant characteristics, OS was not predicted by gender, karyotype, age at SCT, time to SCT, number of chemotherapy courses, donor type, stem cell source, or conditioning regimen. There was a significant association between OS and WBC count at SCT (<10,000/ml: 20 months [95%CI 4.6-NA] vs. ≥10,000/ml: 3.6 months [95%CI 1.9–4.5], $P < 0.0001$), platelet (PLT) count at SCT (>30,000/ml: 18.8 months [95%CI 3.6-NA] vs. ≤30,000/ml: 3.7 months [95%C 1.9–10], $P = 0.05$) and PB blasts at SCT (absent: 79 months [95%CI 2.6-NA] vs. present: 4.5 months [95%CI 3.4–8.6], $P = 0.03$). Stratifying patients according to WBC, PLT, and circulating blasts, we identified four groups with different survival: median OS for patients with 0, 1, 2, or 3 adverse prognostic factors was 79, 10.1, 4.1, and 3.5 months, respectively ($P = 0.004$) (Fig. 1).

Our data confirm that allogeneic SCT can cure a minority of patients with primary refractory AML, and that relapse is the major cause of treatment failure after SCT. In our experience, 3-year OS was lower than that of the MDACC group (18% compared to 39%) but comparable to that reported by the GITMO (10%) [2] and significantly superior to survival after salvage chemotherapy (2–5%) [1,3]. Jabbour et al. found higher WBC, lower PLT, and higher BM blasts percentage at SCT to be associated with superior OS, but did not define any cutoff value [1]. In the setting of unrelated donor transplant for AML primary refractory to various induction strategies (conventional 3 + 7 or HDAC-based regimens), Craddock et al. identified number of chemotherapy courses before SCT (>2) and BM blasts percentage (above a median of 38.5%), along with patient CMV serostatus, as predictive factors for OS [4]. We found that WBC count <10,000/ml, PLT count >30,000/ml and absence of circulating blasts predict superior long-term outcome after SCT. If confirmed in larger studies, this finding may help in designing a simple pre-SCT score to identify AML patients primary refractory to intensive induction chemotherapy that could maximally benefit from the transplant procedure.

Author Contributions

M.M. and M.T. designed the study, collected and analyzed the data, and wrote the manuscript; F.P. A.S., and A.G. contributed to patient care and collection of data; R.F. edited the manuscript. All authors approved the submission of the manuscript.

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References

1. Jabbour E, Daver N, Champlin R, et al. Allogeneic stem cell transplantation as initial salvage for patients with acute myeloid leukemia refractory to high-dose cytarabine-based induction chemotherapy. Am J Hematol 2014;89:395–398.
2. Todisco E, Ciceri F, Oldani E, et al. The CIBMTR score predicts survival of AML patients undergoing allogeneic transplantation with active disease after a myeloablative or reduced intensity conditioning: A retrospective analysis of the Gruppo Italiano Trapianto Di Midollo Osseo. Leukemia 2013;27:2086–2091.
3. Ravandi F, Cortes J, Faderl S, et al. Characteristics and outcome of patients with acute myeloid leukemia refractory to 1 cycle of high-dose cytarabine-based induction chemotherapy. Blood 2010;116:5818–5823.
4. Craddock C, Labopin M, Pillai S, et al. Factors predicting outcome after unrelated donor stem cell transplantation in primary refractory acute myeloid leukemia. Leukemia 2011;25:808–813.

Umbilical cord blood transplantation induces a durable remission in hepatosplenic gamma-delta T cell lymphoma with associated hemophagocytic lymphohistiocytosis

To the Editor: Umbilical cord blood transplantation is an alternative for hematopoietic cell allografting when Human Leukocyte Antigen compatible siblings or unrelated donors are unavailable[1,2]. For adults, transplantation using two cord units is frequently necessary [3–5] and literature demonstrates that double umbilical cord blood transplantation (DUCT) yields durable remissions [1,5,6]. Data on DUCT in hepatosplenic gamma-delta T-cell lymphoma with hemophagocytic lymphohistiocytosis (HLH) are limited to case reports [7,8]. We describe a 22-year-old woman with hepatosplenic gamma-delta lymphoma with hemophagocytosis treated with DUCT.

She presented with B-symptoms, severe anemia, and thrombocytopenia. Bone marrow (BM) flow-cytometry showed an abnormal T-cell population of intermediate size expressing gamma-delta T-cell receptor (coexpression of CD45 and CD3, aberrant expression of CD16 and CD56, intermediate CD2 and CD7, decreased CD8 and aberrant loss of CD5 expression). Cytogenetics showed a female karyotype. She had hepatomegaly, splenomegaly (25 cms), but no radiologic evidence of lymphadenopathy. Splenectomy showed diffuse infiltration by atypical T-cells with identical BM phenotype. FISH of splenic cells showed rearrangement or extracopies of 7q31 but no Epstein–Barr virus. She had elevated liver enzymes and lactate dehydrogenase 2217 (range: 313–618) U/L. Serum ferritin level was 12100 (range: 6–137) ng/mL. Serology for hepatitis B, C, HIV I/II, and HTLV I/II were negative. BM biopsy showed hemophagocytosis. She received three cycles of etoposide, solumedrol, cytarabine, and cisplatinum; but due to persistent fevers, elevated ferritin, and elevated triglycerides, therapy was changed to ifosfamide, carboplatin, and etoposide, given for two cycles. Fevers persisted and repeat BM biopsies showed low-level

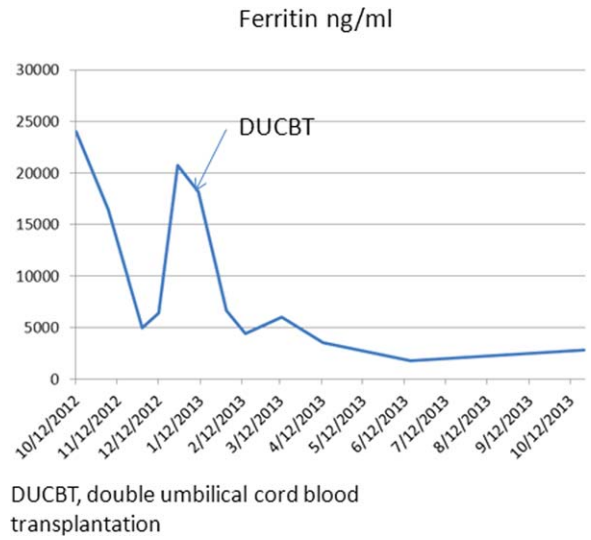

Figure 1. Ferritin levels in ng/mL over time. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]