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Pre-transplantation iron chelation in patients with MDS or acute leukemia and iron overload undergoing myeloablative allo-SCT

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Multiple studies have suggested that iron overload is associated with increased treatment-related mortality after myeloablative allogeneic hematopoietic SCT (MA-HSCT).[1–4] To test the hypothesis that peri-HSCT chelation is feasible, we conducted a pilot clinical trial in patients with myelodysplastic syndrome (MDS) or acute leukemia undergoing MA-HSCT.

The study was designed on the following premises: it appears that patients with iron overload are at increased risk of early mortality (within 3 months of transplantation);[1] infectious risk seems to be responsible for most of this increased mortality;[2,4,5] labile iron (as opposed to parenchymal iron) is known to be significantly increased by myeloablative conditioning[6] and may be the most relevant iron form in effecting toxicity. We therefore hypothesized that the deleterious effect of iron after HSCT may be mediated by labile iron, and that chelating the labile component around the time of conditioning could mitigate the adverse impact of iron overload. Iron chelators can rapidly chelate labile iron (much more rapidly than parenchymal iron). We therefore administered deferoxamine from the time of enrollment (at least 2 weeks prior to the transplantation date) until day −1. We stopped at day −1, reasoning that (1) this would cover the period of cytotoxic therapy and greatest release of labile and non-transferrin bound iron; and (2) this would maximize safety in this pilot study, rather than administering deferoxamine through the early post-transplant period when infectious complications (which may be promoted by deferoxamine) are frequent.

Adult patients with AML, ALL or MDS scheduled for MA-HSCT who had both a serum ferritin ≥1000 ng/mL and a liver iron content >5 mg/g dry weight (mg/gdw), based on hepatic $T2^*$ measurement, were offered enrollment on this study. Patients received deferoxamine IV or SC over 8–12 h at a dose based on the ferritin index.[7] The starting dose of deferoxamine was calculated as serum ferritin ×0.025, capped at 50 mg/kg per day and adjusted every 2 weeks to maintain the ferritin index ≤0.025. Starting 2 weeks after the beginning of treatment, patients also received oral vitamin C 100–250 mg daily. When patients were admitted for HSCT, they continued to receive deferoxamine IV until day −1. MA-HSCT was performed in accordance with institutional guidelines, and study

CONFLICT OF INTEREST

The authors declare no conflict of interest.

assessments as previously published.[8] Labile plasma iron (LPI) was measured using the FeROS assay (Afferix Ltd, Ashkelon, Israel). Informed consent was obtained from all patients. IRB approval was obtained from the Office for the Protection of Research Subjects at Dana-Farber/ Harvard Cancer Center; the study was conducted in accordance with the principles of the Declaration of Helsinki and registered at ClinicalTrials.gov (NCT00658411).

Five patients were enrolled, after which the study closed for slow accrual. Median age was 49 years (range, 20–52 years). Four had AML and 1 had MDS. The median serum ferritin level before HSCT was 3746 ng/mL (range, 2879–7493 ng/mL; upper limit of normal, 400); median transferrin saturation was 87% (range, 47–96%); median liver iron content 12.9 mg/ gdw (range, 5.2–15 mg/gdw.1; upper limit of normal, 1.8); and median cardiac $T2^*$ (with values <20 ms suggesting cardiac iron overload) 61 ms (range, 37–157 ms). For all patients, deferoxamine was administered at 50 mg/kg/d (the maximum allowed dose on this study) for a median of 19 days (range, 12–34 days). There were no serious adverse events due to deferoxamine except for one patient who developed transient hypotension during conditioning and briefly required vasopressor support. The deferoxamine was held and further radiation omitted, and the patient recovered uneventfully. The median change in serum ferritin level between pre- and post-chelation was −901 ng/mL (range, −5109 to +210 ng/mL). For the four patients who had liver MRI before and after chelation (the fifth patient was on chelation for only 12 days and per protocol did not get a repeat MRI), there was no reduction in liver iron content between pre- and post-chelation (median change 0 mg/ gdw). Four of the five patients had no detectable LPI before chelation started; the fifth patient had a pre-chelation LPI of 0.4 units (with low-positive being 0.4–0.6 units, and positive being >0.6 units). At the onset of conditioning, no patient had detectable LPI. However, despite continuing deferoxamine through conditioning, two out of five had positive LPI at the end of conditioning (with values of 1.6 and 1.7 units).

At a median follow-up of 20 months (range, 14–22 months), no patient has relapsed or died; estimated 2-year OS and PFS are both 100%. Only one patient developed grade II acute GVHD, and no patient developed grade III/IV acute GVHD. The incidence of chronic GVHD was 40%. No patient developed VOD.

We conclude that peri-HSCT chelation is a challenging endeavor. The necessity of identifying candidates and screening them with MRI and the need for home administration of deferoxamine, which occured at a time when patients were often recovering from the toxicities of their prior treatment and preparing for their upcoming transplantation, made it very difficult to recruit patients for our chelation trial in the narrow time window between the end of their therapy and the time of HSCT. This emphasizes the need to consider iron-overload issues from the time of diagnosis and throughout the treatment course for patients with acute leukemia and MDS, rather than only at the time of transplantation. Moreover, the hypothesis that deferoxamine administered intermittently just before and during conditioning could prevent the increase in LPI was not borne out by our data. Measurement of LPI is in itself challenging, and the kinetics of LPI chelation with deferoxamine may not allow a durable effect (in particular, we measured post-chelation LPI after the end of deferoxamine administration, which may have allowed a rebound in LPI); so it is possible that with different LPI measurement protocols, and using other chelators or modes and schedules of chelation, a more convincing reduction in LPI may be obtained. Future chelation trials could use a chelation strategy that allows more durable LPI control than intermittent deferoxamine (such as deferasirox or a continuous infusion of deferoxamine), and continue treatment past stem cell infusion when LPI may still be elevated. Nonetheless, and despite the premature closure of the chelation study, it is intriguing that the outcomes of HSCT in those five patients were very good, with no death, relapse, VOD or severe acute

GVHD. The number of patients is far too small to draw reliable conclusions, but leaves open the tantalizing possibility that deferoxamine or other iron chelators, which have already shown possible direct anti-leukemic activity,[9,10] may yet find a role in HSCT, possibly through mechanisms independent of direct labile or parenchymal iron chelation.

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