*Disorders of Iron Metabolism*

## The relationship between transferrin saturation and erythropoiesis during stem cell transplantation

**Ninety-seven percent of 81 patients had a transferrin saturation (TS) level >80% from day 0 of their stem cell transplant. This phenomenon was inversely related with reticulocyte count changes ($p$<0.0001). The time with a TS > 80% was predicted by reticulocyte recovery ($p$=0.031) in multivariate analysis. The kinetics of TS is a direct consequence of erythropoietic activity during stem cell transplantation.**

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Little is known about the behavior and causes of increased transferrin saturation (TS) during stem cell transplantation (SCT).[1] We studied 81 patients (43 men, 38 women, median age 54 years, range 19-70, ECOG score ≤2) in complete remission from hematologic malignancies, all of whom underwent a peripheral blood SCT. Their diagnoses were acute leukemia (n=22), chronic myeloid leukemia (n=2), myelodysplastic syndromes (n=5), multiple myeloma (n=28) and non-Hodgkin's lymphoma (n=24). The status of disease was first complete remission in 33 and ≥ second complete remission in 48. The SCT was autologous in 50 patients, allogeneic in eight and allogeneic with reduced-intensity conditioning (RIC-SCT) in 23. Erythrocyte sedimentation rate, serum iron (SI), total iron binding capacity (TIBC), TS, ferritin, aspartate amino transferase (AST), absolute reticulocyte count and reticulocyte fractions were measured serially in each patient. A first sample was taken pre-SCT, and the others were taken twice weekly from day 0 until the absolute neutrophil count was ≥500/μL. *HFE* genotype was determined in all cases.[2] The ablative conditioning regimens used were cyclophosphamide plus total body irradiation (n=17), cyclophosphamide–busulphan (n=2), CBV (n=10), BEAM (n=10) and high-dose melphalan (n=19) and fludarabine-based in the RIC-SCT group.[3] Differences between categorical variables and means of continuous variables were analyzed by the $\chi^2$ test and the Mann-Whitney U test, respectively. Relationships between categorical and continuous variables were studied by analysis of variance. Kaplan-Meier and Cox regression analyses were used to perform, respectively, univariate and multivariate comparisons of the amount of time patients maintained a TS ≥80%. Results were considered statistically significant when $p$ values were less than 0.05.

Pre-SCT values of SI, TIBC and TS were normal. Only six patients had a TS>80%. Mean pre-SCT ferritin concentration was high (954 μg/L, SD 913). The C282Y genotypes were wild-type (n=76) and heterozygous (n=5). There were no C282Y homozygotes. The H63D genotypes were wild type (n=41), heterozygous (n=36) and homozygous (n=4). In 79 patients (97%), the TS level at day 0 was >80% and it remained at this level for a median of 9 days (CI 95% 8–10 days). The increase in TS paralleled a rise in SI and both increases correlated with a synchronous decrease in the absolute number of reticulocytes. All three parameters normalized synchronously ($p$<0.001) (Figure 1). The AST levels were normal throughout follow-up. To investigate which variables were related with the time patients maintained a TS >80%, we included the clinical and pre-SCT biological variables previously cited in a multivariate model. Two variables were significant: days before the start of high fluorescence reticulocyte (HFR) recovery ($p$=0.031) and autologous *vs* allogeneic SCT ($p$=0.033). The type of transplant with the longest period of TS >80% was allogeneic RIC-SCT (11 days, 95% CI 9.9–12.1), the second conventional allogeneic SCT (9 days, CI95% 6.4–11.6) and the third autologous SCT (7 days, CI 95% 6.1-8); $p$=0.0009. These differences correlated with different times to begin HFR recovery, being 12 days for RIC-SCT, 11 days for conventional allogeneic SCT and 10 days for autologous transplants ($p$=0.08) (Figure 2).

There are several possible explanations for the changes

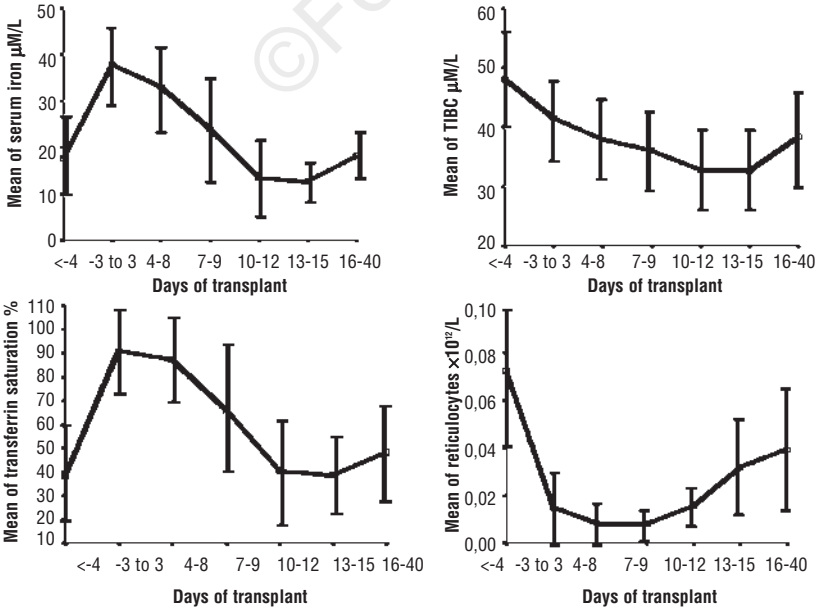


**Figure 1.** Evolution of means (and SD) of serum iron, TIBC, TS and absolute reticulocyte counts in the 81 patients studied. Changes are significant over time ($p$<0.001) in all cases.

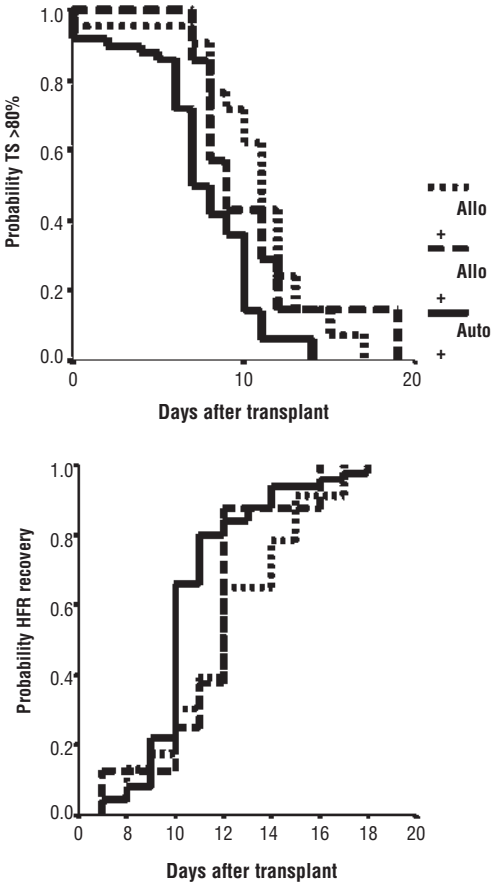


**Figure 2.** Graph showing probability of TS >80% and days to recovery of high fluorescence reticulocytes (HFR) according to the type of transplant (autologous: continuous line, conventional allogeneic: dashed line, allo RI-SCT: clotted line). $p$=0.0009 and $p$=0.08, respectively.

in TS during SCT: inhibition of erythropoiesis, tumor cell destruction, a decrease in transferrin synthesis and liver cell damage with a release of iron stores.[4] In our study, only the first cause was responsible for the TS increase. All our patients were in complete remission, thereby excluding tumor cell destruction as a cause. AST levels remained normal throughout the process, ruling out significant liver cytolysis. Although a TIBC decrease was observed, this change was not present during the first week when the maximum rise in TS occurred. Erythropoiesis is the main physiological acceptor of daily-recycled body iron and its suppression by chemotherapy stops clearance and utilization of transferrin-bound iron leading to raised TS. The mirror image of the graphs showing TS and absolute reticulocyte counts plotted against time supports this hypothesis (Figure 1). Erythropoietic activity in these patients starts 6-7 days before the HFR rise in peripheral blood (bone marrow transit time), exactly when TS declines. The number of days before HFR recovery begins predicts the number of days with TS>80% ($p$=0.03). Our results agree with those of Bradley *et al*. using conventional chemotherapy and other methods.[5] TS levels <80% and erythropoiesis recovered earlier following autotransplants than following allotransplants ($p$=0.033, RR=1.75). An inhibition of erythropoietin secretion has been attributed to the use of cyclosporine.[6,7] This effect can be maximum in RIC-SCT. Cyclosporine is started on day –7 in this transplant modality, and not on day –1 as usual. TS changes after conditioning seem to be independent of body iron. Measures to control TS should be directed towards stimulating erythropoiesis or TIBC with transferrin infusions.[8] Measures to decrease iron overload[9] will probably be unsuccessful.

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