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Fulminant hepatitis in aplastic anemia: hepatitis G or ALG?

After reading the article by Killick *et al*[1] in the February 1997 issue of *Bone Marrow Transplantation* we wish to report a case of aplastic anemia and fulminant hepatic failure. An 18-year-old girl with a diagnosis of severe aplastic anemia was admitted to the Department of Hematology, Ibni Sina Hospital, Ankara University. She received cyclosporine (10 mg/kg/day 6 months), antilymphocyte globulin (ALG) (Pasteur Merieux, Lyon, France) (20 mg/kg/day 8 days), prednisolone (2 mg/kg/day 8 days) and GM-CSF (5 μg/kg/day) according to the protocol arm to which she was assigned. Two days after the last dose of ALG she developed bone pain and abdominal pain, and her transaminases and bilirubin levels which were normal before therapy started to rise dramatically. ALT levels rose to 2837 U/l, AST levels increased to 4796 U/l and bilirubin levels rose to 23.46 mg/dl. Urinary output diminished followed by a rise in creatinine and blood urea nitrogen levels. The maximum level for creatinine was 7.6 mg/dl. She died 3 days after this. Hepatic biopsy revealed massive hepatic necrosis. G virus RNA was detected using RT-PCR as described before.[2] Hepatitis B antibody was positive and serological markers for HCV and HAV were negative at that time. She was hepatitis B antibody positive before treatment. It is premature to say that this hepatic failure resulted from G hepatitis because a case of severe hepatic failure that occurred after the administration of ALG + cyclosporine has been reported.[3] Also, hepatitis G might or might not be the cause of aplastic anemia in this patient as described before.[4,5] Nevertheless, this is a documented case of severe hepatitis in the presence of G virus. Recent articles indicate that G virus is not a cause of hepatitis, and does not alter the clinical course of hepatitis C.[6,7] We still feel that one must be cautious in interpreting G virus until it is clearly documented that it is innocent.

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Is there a relationship between G-CSF response to conditioning regimen and engraftment after bone marrow transplantation?

Busch *et al*[1] recently published an article in the Journal. In a selective group of patients with CML, they showed that patients with later engraftment presented higher G-CSF levels than the patients with earlier engraftment. While both groups started with identically low G-CSF levels 1 day prior to bone marrow transplantation, levels differed at day +1 after bone marrow transplantation and this difference continued until day +10. It has been shown that peripheral stem cell infusion has a cytokine triggering effect.[2] We have previously reported very high levels of G-CSF following peripheral blood stem cell transplantation used to rescue engraftment failure (Figure 1).[3] In the study by Busch *et al*, the difference in mean G-CSF levels at day +1 may be caused by differing amounts of the infused cell dose. In our study, serum G-CSF which was measured by the same enzyme immunoassay principle (Amgen Diagnostics, Thousands Oaks, CA, USA) reached its highest levels at day 0 just after the end of conditioning. In contrast to the finding of Busch *et al*, the G-CSF levels at day 0 were lower in three of our patients with engraftment failure compared to those with successful engraftment (Figure 1). This finding is in concordance with Cairo *et al*'s results.[4] Our

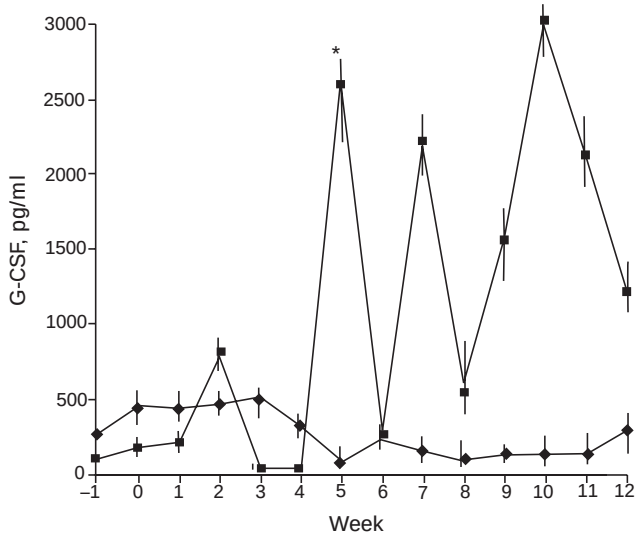


Figure 1 Serial weekly change in serum G-CSF levels. (◆), uncomplicated patients $n = 14$; (■), patients with engraftment failure $n = 3$. *Indicates one of the samples drawn after second transplantation by peripheral blood stem cell infusion.

study differs from Busch's study by inclusion of patients with various diagnoses ($n = 19$) (ALL ($n = 7$), ANLL ($n = 5$), CML ($n = 5$) and aplastic anaemia ($n = 2$)). We used BU + CY or CY + TBI as conditioning regimen which were similar.

In the article the authors found extremely high G-CSF levels in some patients, but gave no explanation. In our previous study, one of the highest levels of G-CSF (>3000 pg/ml) in bone marrow transplantation patients was observed during a febrile episode. Mean G-CSF levels were also significantly higher in samples from febrile periods than in samples without fever, 585 ± 272 and 328 ± 180 pg/ml ($P < 0.05$), respectively.[5] Busch *et al* suggested that high G-CSF levels at days +1, +4, +7 and +10 were predictive of late engraftment. However, they did not measure the baseline levels just prior to the conditioning regimen. In patients with blastic phase the G-CSF levels may increase as seen in our study. In their study, there is no information about G-CSF levels during the first 10 days according to either type of conditioning regimen or type of donor marrow source. Consequently no data are available regarding engraftment rate and donor type.

Busch *et al* did not determine the G-CSF levels in healthy people, which may be an important factor. We found detectable G-CSF levels in 30% of healthy people with a mean of 62 pg/ml (range 0–230 pg/ml).[5] Also, the standard deviation (469 ± 1364 pg/ml) found in the study by Busch is rather high to make clear assumptions. The fluctuations seen in Figure 1 prevented us from making clear statements and we postulated that early G-CSF monitoring may predict engraftment failure and allow early manipulations with CSF. It has also been shown by Migliaccio *et al*[6] that G-CSF bioactivity is not detectable in bone marrow supernatants of patients who failed to engraft. Although Busch *et al* claim that early G-CSF levels affect engraftment they have not analyzed patients with engraftment failure. In our study, there were three patients with absolute engraftment failure. In those patients we observed considerably lower initial G-CSF levels during the first 3 weeks (weeks −1, 0 and 1) and high fluctuating levels in the following weeks (Figure 1).

What can cause high G-CSF levels in patients with late engraftment? Is this a result or a cause? T cell-depleted transplants should not be used as a model for comparison because of G-CSF production by T cells. If a patient has delayed engraftment, it may coincide with higher risk of infections which are known to stimulate G-CSF production. For example, in the study, there is no clear explanation for the high G-CSF levels seen in patient No. 7. We have observed a negative correlation between WBC and G-CSF levels in uncomplicated transplants. Busch *et al* observed the same correlation only in patients with early engraftment. Both findings may support the idea that high G-CSF levels in late engrafting patients might be the result of complications like infections. In conclusion, we do not agree with the proposed influence of high G-CSF plasma levels as predictive of late engraftment. It is very difficult to link a single parameter (G-CSF level) to engraftment which is a complex phenomenon.

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