

Mismatched Bone Marrow Transplantation for Severe Aplastic Anaemia after Liver Transplantation for Associated Acute Liver Failure

Dear Editor,

We report the first case of same donor liver and bone marrow transplantation (BMT) for acute liver failure due to non A-E hepatitis (NAEH) associated with severe aplastic anaemia (AA).

Case Report

A previously well 10-year-old Vietnamese boy with exanthematous fever, jaundice (Alanine aminotransferase 688 U/L, Aspartate aminotransferase 340 U/L) and pancytopenia (Haemoglobin 4.2 g/dL, WBC $1.7 \times 10^9/L$, and platelets $< 20 \times 10^9/L$) developed grade 4 hepatic encephalopathy at 10 weeks of illness.

Extensive workup failed to reveal the aetiology. At 11 weeks of illness, a liver transplantation (LT) (segments 5 to 8) was performed, mother being the donor. Histology of the native liver showed massive necrosis.

The liver function normalised but there was persistent febrile neutropenia (ANC $0.07 \times 10^9/L$, RBC $2.27 \times 10^{12}/L$, and platelets $28 \times 10^9/L$) (Fig. 1) due to severe AA (marrow cellularity $< 5\%$). The treatment of such hepatitis-associated AA (HAA) using immunotherapy entails a time lag (median 60 to 80 days) to myeloid response, even with accelerated regimes. There is also a higher risk of relapse, bone marrow aplasia, clonal disorders and, if the conditioning includes irradiation, secondary malignancies.^{1,2} Therefore, an urgent bone marrow transplant (BMT) was planned.

With no available matched sibling or unrelated donor, we pursued a partial matched BMT from the mother (homozygous mismatch at HLA A, antigen mismatch at HLA B); there being a lower risk of post-BMT red cell aplasia due to identical ABO match. A reduced-intensity, liver-protective preparative regimen [fludarabine ($120 \text{ mg}/\text{m}^2$), cyclophosphamide ($10 \text{ mg}/\text{kg}$), anti-thymocyte globulin (ATG) ($90 \text{ mg}/\text{kg}$) and rituximab ($375 \text{ mg}/\text{m}^2$)] with subsequent ex-vivo T-cell depleted donor bone marrow ($\text{CD}34 \ 3.4 \times 10^6/\text{kg}$; $\text{CD}3 \ 0.1 \times 10^6/\text{kg}$) was administered. Graft versus host disease (GVHD) prophylaxis consisted of methotrexate ($10 \text{ mg}/\text{m}^2 \text{ day}+1$, $5 \text{ mg}/\text{m}^2$ on day+6 and day+11 after BMT) in addition to post-LT immunosuppression.

Although there was initial myeloid engraftment (day 14, 100% donor chimerism), the bone marrow graft was eventually rejected (day 20) with subsequent spontaneous myeloid recovery (32 to 41 days following BMT) (3% donor chimerism).

Cytomegalovirus (CMV) reactivation on day 52 following BMT was treated by oral valganciclovir (450 mg bid) for 4 weeks until seronegative. Tacrolimus was continued at a dose of 2 mg bid for a year whereas prednisolone was tapered from 15 mg to 10 mg daily. There was no liver allograft morbidity related to the BMT regimes.

Follow-up revealed peripheral donor chimerism (3%) at 9 months and normal blood pressure, neurology, liver

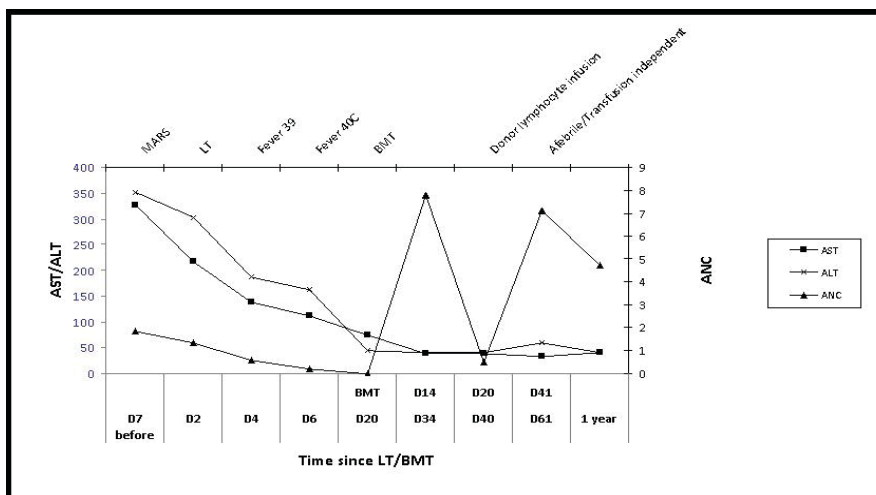


Fig. 1. Timeline of events vis-a-vis trending of liver function and febrile neutropenia.

MARS: Molecular adsorbent recirculating system; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; ANC: Absolute neutrophil count; LT: Liver transplantation; BMT: Bone marrow transplantation

function, renal function and full blood count at 1 year.

Discussion

The first report of NAEH and AA following LT was, respectively, in 1955 by Lorenz and Quaiser and in 1987 by Stock.¹ The incidence of AA associated with acute hepatitis of known aetiology is 0.07% and following LT for such known hepatitis is 0.007%.^{1,2} However, the incidence of AA is much higher in association with NAEH (33% in children and 5% in adults) and following LT for NAEH (28%).¹

The proposed pathogenesis is that there is indirect bone marrow suppression and hepatitis due to viral induced proliferation of activated CD8 cells.^{1,2}

Bone marrow dysfunction rarely precedes but usually occurs either with the hepatitis or 1 to 7 weeks after liver transplantation.^{1,2} The association of AA and NAEH is commoner in male adolescents.¹ Spontaneous myeloid recovery on maintenance immunosuppressants takes up to 6 months and has 50% mortality due to infections and bleeding.^{1,2}

The specific treatment options are either immunotherapy (additional immunotherapy with ATG or intensification of maintenance immunosuppression; with or without haematopoietic growth factors) or BMT from a HLA identical sibling.^{1,2} Both have similar (80% to 90%) 5-year survival rates.^{1,2} With immunotherapy, the response rates are 70% to 80% with likelihood of an improvement in liver function.^{1,2} But, there are drawbacks (vide supra). Therefore, HLA matched sibling BMT is the first line treatment for severe HAA.²

The BMT preparative regimes are well tolerated by the liver grafts without increased incidence of GVHD, veno-occlusive disease or infections.^{1,2}

Since, only 20% to 30% of the patients have an identical sibling donor,^{1,3} matched unrelated BMT is the next option. Mismatched transplants from family donors may have similar survival; but there is a higher risk of either GVHD (for HLA mismatched class II antigens) or graft failure (for HLA mismatched class I antigens).³ Prophylaxis against GVHD and T cell depletion for marrow engraftment has been employed with some success.³ Post-grafting cyclophosphamide without ex-vivo T cell depletion is an excellent alternative. At the time when we were treating our patient; and as of now, data is still limited to cancer indications and a case series of 3 patients with non-cancer indications.⁴

Alternately, transplantation of autologous cord blood or sibling-identical haematopoietic stem cell transplantation (HSCT) is shown to achieve successful stem cell rescue (8 reported cases).^{5,6}

Interestingly, operational tolerance is not unknown in such situations.⁷

Conclusion

In conclusion, for severe AA following LT, in the absence of matched donors, it is debatable whether to pursue an urgent BMT with the best available family donor. This and the role of autologous cord-cell transplantation need further clinical investigation.

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