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Orthotopic Liver Transplantation for Treatment of Sinusoidal Obstruction Syndrome: A Case Report

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Abstract

We here report the case of successful orthotopic liver transplantation (LT) following acute liver failure (ALF) related to sinusoidal obstruction syndrome (SOS). This syndrome is one of the main causes of death early after bone marrow transplantation (BMT); LT seems to be an effective treatment of the most severe forms of SOS but no official recommendations exist about this subject. With this clinical case we would like to show that after careful patient selection and appropriate timing, LT for treatment of severe SOS is safe and effective.

Keywords

Acute liver failure, Sinusoidal obstruction syndrome, Veno-occlusive disease, Orthotopic liver transplantation

Abbreviations

ALF: Acute Liver Failure; AST: Aspartate Transaminase; CT: Computed Tomography; BMT: Bone Marrow Trasplant; EBMT: European Society for Blood and Marrow Transplantation; EBV: Ebstein Barr Virus; GVHD: Graft Versus Host Disease; HCT: Hematopoietic Cell Transplantation; ICU: Intensive Care Unit; LT: Liver Transplantation; MELD: Model for End stage Liver Disease; MOF: Multi Organ Failure; MMF: Mofetil Mycophenolate; POD: Post-Operative Day; PT: Prothrombine Time; PTLD: Post-Transplant Lymphoproliferative Disease; RRT: Renal Replacement Therapy; SOS: Sinusoidal Obstruction Syndrome; TIPSS: Trans-jugular Intra-hepatic Porto-Systemic Shunt; VOD: Veno-Occlusive Disease

Introduction

SOS, also known as veno-occlusive disease (VOD), is a rare but fearsome complication of BMT leading, in worse cases, to ALF and death. Hepatic transplantation was first proposed for treatment of severe and refractory SOS more than twenty years ago: However only few cases were reported in literature and no official recommendation exists about this subject. Whether LT is safe for treatment of severe refractory SOS is unknown: However, according to recently published case reports, hepatic transplantation seems feasible and more effective than medical treatment alone. None the less correct timing of LT is crucial: Post-operative infectious complications and graft versus host disease (GVHD) are the main concerns. We here report the case of a successful orthotopic LT for SOS-related ALF: Transplantation was successful and no major adverse event occurred after one year follow up.

Case Presentation

Our 27-year-old patient was diagnosed with acute myeloid leukemia. BMT was carried out (day 0) in *Centre Hospitalier Lyon Sud* teaching hospital after induction by Idarubicin and Cytarabin and consolidation by Cytarabine, Busulfan and Endoxan: Treatment allowed full cytologic remission. GVHD prophylaxis included Ciclosporine and Mofetil mycophenolate (MMF). Medullary aplasia lasted three weeks after BMT and was complicated by several undocumented sepsis and a non-severe *Clostridium difficile* colitis. Abdominal pains and thrombocytopenia appeared on day 23; concomitantly, signs of hepatic dysfunction were noted with appearance of cytolysis, cholestasis and diminished synthetic func-

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tions; cytolysis (predominantly on the aspartate transaminase, AST) peaked on day 30 reaching values tenfold as high as normal; by this time total bilirubin was 146 µmol/l. Prothrombine time (PT) fell down to 20% on day 33. An abdominal computed tomography (CT) showed signs of portal hypertension (splenomegaly, mild ascites and peri-portal edema). There was no sign of hepatic encephalopathy. SOS was immediately suspected: Ursodeoxycholic acid and Defibrotide were therefore started without delay. Unfortunately patient conditions quickly worsened: hepatic encephalopathy, respiratory and renal failure appeared and patient needed transfer to the local intensive care unit (ICU).

Owing to worsening liver function and evolution to fulminant hepatic failure despite optimal medical treatment, patient was transferred to our abdominal transplantation center on day 33 in order to confirm diagnosis and consider LT. A trans-jugular liver biopsy was performed and confirmed SOS/VOD diagnosis; it also allowed exclusion of hepatic GVHD. By this time, patient met both Beaujon and King's college criteria for LT and model for end stage liver disease (MELD) score was 37. He finally underwent orthotopic LT 38 days after BMT. Surgery was uneventful and no immediate complication occurred. Patient was extubated on post-operative day (POD) 2 and renal replacement therapy (RRT) was discontinued on POD 10 after full renal function recovery. Initial immunosuppressive treatment included MMF, Tacrolimus and low dose corticosteroids: In order to prevent myelotoxicity, MMF was discontinued after a few weeks. Defibrotide was discontinued immediately after LT after 15 days of treatment, as recurrence of post BMT SOS on the transplanted liver has never been described.

Patient was discharged from our ICU on POD 23 and he was able to leave hospital on POD 30. The late post-operative period was characterized by an Epstein-Barr virus (EBV) reactivation requiring polyvalent immunoglobulin administration. The systematic follow up showed a new recurrence of EBV infection two months after LT; it was associated with four isolated hepatic nodules: a biopsy was performed and lead to diagnosis of EBV-induced post-transplant lympho proliferative disease (PTLD). Full remission was obtained after discontinuation of corticosteroids and four injections of Rituximab. No other major complication occurred one year after bone marrow and liver transplantations. The systematic liver biopsy one year after LT showed no sign of recurrence of SOS; no sign of liver graft rejection was noted either but unfortunately signs of hepatic GVHD started to appear.

Discussion

SOS is a not uncommon complication of BMT (incidence ranges from 5% after autologous HCT to 15% after allogenic HCT) leading, in worse cases, to acute liver failure (ALF) and death [1-3]. Very severe forms account for about 15-20% of all SOS and without appropriate treatment mortality may be as high as 80-90% [4]. Defibrotide has been shown effective in both prevention and treatment of SOS [4-8] and, to date, it is the sole recommended treatment [9]. Despite early treatment, mortality in very severe forms, remains as high as 61.8% [8]. More invasive treatments such as Trans-jugular intra-hepatic porto-systemic shunt (TIPSS) [10] and LT [11] have therefore been proposed. TIPSS have first been reported in literature in 1996 [12] for the management of severe VOD/SOS; according to a recent series [10], mortality after TIPSS seems unacceptably high, nevertheless a transient improvement in hepatic and renal function was noted. TIPSS might therefore be considered as a bridge therapy to transplantation, in order to enhance LT outcome. Such a strategy has already been described for fulminant Budd-Chiari syndrome [13].

Hepatic transplantation for treatment of life-threatening VOD/SOS has been performed with variable outcomes since the early '90s. In 2008 a review of the literature [11] showed a high mortality rateafter LT: Mortality was mainly related to septic complications. Trying to reduce immunosuppressive treatment should therefore be the cornerstone of the peri-operative care of these patients. This could be achieved through cautious patient selection and lighter immunosuppression associated with close patient surveillance. Our patient did not suffer from early septic complications, however his immunocompromised state lead to EBV reactivation and PTLD. PTLD being linked to the depth of immunosuppression [14], a high rate of PTLD should be expected in this particular population. Finally, the one-year follow up liver biopsy showed no recurrence of SOS after transplantation. Indeed SOS is linked to the endothelial damage caused by the induction regimen. But it must kept in mind that some immunosuppressive treatments, such as Tacrolimus [15] and Azathioprine [16] can be implied in the genesis of SOS. SOS can therefore recur on the liver graft.

To conclude, SOS is a quite rare but dreadful complication of stem cell transplantation. Mortality remains unacceptably high despite early appropriate medical treatment. Our experience shows that LT is safe and feasible for treatment of life threatening SOS in patients with good prognosis BMT. Optimal timing of LT is unknown but cautious patient selection is of main importance: Candidates to LT should have good hematological prognosis, good BMT engraftment and, whenever possible, histologically proven severe form of SOS. Medical care after LT should be stressed on preventing and optimally treating infections. Data on this subject remain

scarce and more research is needed in order to identify prognostic factors that could help us predict short and long term outcome after LT.

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