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CASE REPORT

Is it time to revisit contraindications to organ donation from donors with a JAK-2 mutation? Safe use of a liver allograft from a donor with essential thrombocythaemia

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Summary

Transplantation can cure end-stage liver disease and hepatocellular carcinoma. However, the balance of organ demand and provision is heavily tipped to the detriment of patients. Patients awaiting transplantation rely on the greater use of marginal donors that may carry a risk to the recipient. UK authorities have decreed donor haematological malignancy an absolute contraindication. The authors describe the first report of a patient being safely transplanted with a liver from a donor who suffered from JAK2 V617F mutation-driven essential thrombocythaemia to a patient with a critical burden of hepatocellular carcinoma. A year after transplantation, the patient has neither evidence of acquisition of the donor's pathology, nor evidence of carcinoma recurrence. The case highlights the responsibility of the recipient team to maximize the use of organs by expert risk assessment. Dissemination of experience should inform future decisions, benefit patients and bolster utility in an era of growing waiting-list mortality.

Introduction

Despite the success of liver transplantation, it cannot be offered with utilitarian abandon. The scarcity of suitable postmortal donors has hampered the delivery of this effective cure, with resultant increases in waiting times, and wait list mortality.

One way to combat the burgeoning demands on the organ donation programme has been to expand the available donor organ pool by the use of 'extended criteria' grafts. The utility of 'riskier' donors is accountable to a definition of acceptable outcome after liver transplantation, which advocates that liver transplantation should deliver a comparable and acceptable survival regardless of indication

for transplantation. This requires the recipient's risk of wait list mortality or drop out to be balanced against the risk (and benefit) portended by the donor graft. It is accepted that all donors carry some risk to the recipient, and this risk is not absolute, but should be perceived as a continuum, and thus the absolute criteria contraindicating donation will change with experience. This learning curve is vital in an era of donor shortages.

Absolute contraindications to deceased organ donation include any cancer with evidence of spread outside the affected organ and active haematological malignancy [1]. Nevertheless, controversies in the relevance of these mandates require the surgeon to weigh-up donor and recipient factors to decide whether to accept an organ. Guidelines should aid, but not replace clinical judgement, and the authors hereby describe the first published case of liver transplantation from a donor with a JAK2 V617F mutation-associated essential thrombocythaemia (ET) to a recipient with HCC who was deemed to be at risk of tumour growth and falling off the waiting list.

Case report

A liver graft offer from a 74-year-old man who had suffered a brain death became available. He had a medical history of ET due to a JAK2 V617F mutation, diagnosed 30 years previously. His platelet count had been stable for 5 previous years on treatment with cytoreductive hydroxyurea. At the time of organ offering, the platelet count was 327×10^9 (normal $150–400 \times 10^9$). There were no clinical manifestations of his disease throughout the course of the diagnosis (thrombotic events or other associated complications). The donor organ was offered to the authors' centre as a fast-tracked offer, having been declined at all other centres in the UK.

In acknowledgement of the guidance from NHSBT, the matter was escalated via local experts on haematological malignancies through to national expert opinion. The risk of transmission of the JAK2 V617F mutation through liver transplantation was deemed to be low (<5%) – based on the well-controlled indolent history, the donor's age and the disease being likely limited to the bone marrow. Furthermore, in the unlikely event of disease manifestation in the recipient, effective cytoreductive treatment is available. The best suitable recipient was chosen by balancing the risk of transmission of a haematological malignancy to the recipient with that of waiting-list mortality and drop out. After an explanatory discussion with the recipient and family, a unanimous informed decision was taken to accept the organ and proceed to transplantation.

The recipient was 69 years old and was initially considered for liver transplantation for a 2.9 cm solitary HCC on the background history of cryptogenic cirrhosis, with diuretic-controlled ascites and Model for End Stage Liver Disease (MELD) score of 11. Having presented with alpha-fetoprotein (AFP) of 2065 kU/l (normal <6 kU/l), the patient underwent trans-arterial chemo-embolization prior to listing. Bridging therapy yielded a partial radiological response and AFP reduced to 22 kU/l. Over 5 months on the transplant wait list, the patient's AFP rose above 200 kU/l and follow-up imaging showed tumour growth to 4.5 cm (unifocal). This patient was deemed best suited to receive the aforementioned offer of a donor organ. The recipient was subsequently discharged 2 weeks following a successful and uneventful transplantation. The explant histology revealed a 1.7 cm HCC with extensive necrosis secondary to embolization with minimal viable tumour remaining and no vascular invasion. The background liver was cirrhotic with nonspecific biliary features. One year into follow-up, the patient is well and free of HCC recurrence. She has not suffered any clinical events or demonstrated any clinical surrogates (thrombocythaemia) to suggest a prothrombotic state. Furthermore, she has twice had negative qualitative assessment for JAK2 V6I7F mutant allele burden. The first sample was tested in the immediate perioperative period as the baseline test, using semiquantitative ASO-PCR and fluorescence-based capillary gel electrophoresis which reliably detects mutation levels above 5%, and the second test was performed 9 months after the transplantation to rule out disease transmission. On this occasion, the test was carried out with a quantitative droplet digital polymerase chain reaction assay, which can reliably detect the mutation if it is present at 0.1% burden.

Discussion

Essential thrombocythaemia is the manifestation of clonal expansion that occurs as a consequence of an acquired somatic mutation which results in the constitutive activation of a tyrosine kinase enzyme, JAK2; the V617F mutation in JAK2 exon 14 is implicated in about 65% of patients with ET. JAK2 V617F mutation-positive ET primarily carries a risk of thrombosis and bleeding. The risk of disease progression to post-ET myelofibrosis is relatively rare compared to other types of myeloproliferative neoplasm [2].

Pathophysiologically, disease transmission to the recipient would require donor myeloproliferative cells from the liver graft to populate healthy bone marrow and hence dominate subsequent thrombopoiesis. This is turn, would require there to have extramedullary haematopoiesis (EMH) in the donated liver. The risk of EMH is undeniable, and with it the risk of transmission of the JAK2 V617F mutation in a megakaryocytic clone. This risk was estimated from the clinical surrogates for disease progression, of which the donor presented none. These were described in the 2008 International Working Group for Myelofibrosis Research and Treatment proposal, in which they designated

anaemia, a leukoerythroblastic peripheral blood picture, increasing splenomegaly, increased lactate dehydrogenase and constitutional symptoms as allied criteria to bone marrow fibrosis to suggest progression [3]. Moreover, of the three myeloproliferative manifestations of a JAK2 V617F mutation, ET harbours the lowest mutant allele burden, and thus probably a lower risk of transmission [4]. Most convincingly, liver biopsy of the donor organ 14 days after transplantation showed no evidence of EMH in the liver.

It follows, the risk of acquired thrombogenicity in our recipient is low in the presence of negative mutational studies and absence of thrombocythaemia [5], and thus, there is no evidence to support antithrombotic therapy beyond our standard of care. Furthermore, the guidance for the use of antimyeloproliferative agents for those deemed to be at intermediate or low risk remains unclear [6,7]. The risk of malignant transformation, (15-year survival 59% for prefibrotic primary myelofibrosis; 80% for ET) [2,7], is deemed to be low for exactly the same reasons.

This case documents the first liver transplantation from a patient with ET. However, it cannot be used as a road map for all JAK2 V617F donors. Primary myelofibrosis carries greater mortality, avidly drives EMH, and would carry an appreciable risk of clonal transmission. PRV is allied to a greater mutant allele burden [3] than ET, although designated clinical surrogates of disease progression can help to estimate the perceived risk of EMH. The authors advocate that each donor be assessed with these factors in mind, and a specialist in the field be consulted to approximate the risk of clonal transmission. Further experience will allow us to accurately define and discuss the potential risk to recipients and consider donors with JAK2 mutation-driven pathology for other indications. Although rare (prevalence for ET 11–42.5 per 100 000; for PRV 0.49–26.9 per 100 000 [8]), any cohort of potential additional organ donors should be embraced.

A similar premise can be applied to the use of organs from donors with solid organ malignancies, whereby the probable risk can be estimated by the detail of the cancer history, and may allow the use of organs from donors with a history of central nervous system, genitourinary tract and breast cancers [9,10].

The case highlights the need for a broad-minded approach to objectively consider the risk to the recipient in individual cases, and the importance of sharing this experience with the wider transplant community so that opportunities to expand the donor pool in an era of growing waiting-list mortality are not missed.

Authorship

DH: wrote report. DH, FC, JB, AME, MTPRP: intellectual contribution, involved in case.

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