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Long term follow-up after liver transplantation from a *JAK2* mutation positive donor

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Introduction

Philadelphia-negative myeloproliferative neoplasms (MPN), including polycythemia vera (PV), essential thrombocythemia (ET), and primary myelofibrosis (PMF), are characterized by the presence of mutations involving the Janus Kinase 2 (*JAK2*), calreticulin (*CALR*) or myeloproliferative leukemia virus oncogene (*MPL*) genes (1). Of these, the *JAK2* V617F gain-of-function mutation is the most frequently found and is present in >95% of patients with PV and in about 60% of those with ET or PMF whereas *JAK2* exon 12 mutations are found in the remaining PV patients (2). *JAK2* V617F somatic mutations have been detected in granulocytes and platelets and therefore they could potentially be transmitted to recipients of solid organ transplants (3) and in fact the presence of the *JAK2* V617F mutation has been detected in otherwise healthy blood donors (4,5).

ET and PV may represent different ends of a genotypic/phenotypic continuum so that life expectancy of patients with PV is reduced compared with the general population, whereas that of patients with ET appears not to be as significantly affected (2). Additionally, the presence of this mutation could potentially have adverse consequences in the graft. Westbrook and colleagues looked at patients transplanted for Budd Chiari syndrome and found the *JAK2* mutations to be associated with a 33% rate of graft loss from thrombosis (6). Given the shortage of organ donors and the fact that the potential consequences of the presence of a *JAK2* mutation are relatively benign, the possibility of considering a *JAK2* positive donor may be of interest, in particular in situations in which the potential recipient has a terminal condition with an expected high short-term mortality.

Methods

Case presentation

We were offered organs from a 54-year-old female donor, blood group A Rh+, who had a 22-year history of ET and who was known to have the *JAK2* V617F mutation and who died of a cerebrovascular thrombosis. The donor was taking anagrelide and previously she had been treated with hydroxyurea and interferon. We transplanted the liver to a 68-year-old male who was A Rh+ with a negative cross-match with the donor. The patient had a history of end-stage liver cirrhosis secondary to alcohol consumption. We disclosed our uncertainty regarding the transmission of ET which we believed would be treatable should it occur and not affect the recipient's longevity. We also disclosed our uncertainty whether the phenotype of MPN might worsen in the presence of immunosuppression. Given his clinical status the patient understood and accepted the risks. The patient underwent an uncomplicated orthotopic liver transplant. Immunosuppression with tacrolimus, mycophenolate and steroids was given according to the institutional protocol. No treatment or prophylaxis was given against MPN.

Laboratory methods

Liver biopsy samples from both donor and recipient, and peripheral blood samples from the recipient were obtained.

DNA was extracted using standard methods.

Utilizing a semi-quantitative real-time polymerase chain reaction (PCR) analysis on a Roche 480 LightCycler (Roche Diagnostics, Risch, Switzerland), mutation specific primers were used in a kit-based assay (*JAK2* MutaQuant; Ipsogen, France) to distinguish between the mutant and normal PCR-amplified *JAK2* alleles, and by comparison with a panel of standardized reference normal and/or mutant DNA samples. This assay allows a sensitive semi-quantitative detection of the mutant *JAK2* allele in genomic DNA. This methodology is estimated to detect as few as 10 copies (<0.01%) of the mutant *JAK2* allele/assay sample.

Clinical course

As expected, PCR analysis of the liver biopsies showed that the donor was strongly positive for the *JAK2* V617F mutation whereas the recipient was negative. A peripheral blood sample from the recipient obtained immediately before the transplant was negative for the *JAK2* V617F mutation whereas another sample obtained within the first 24 hours after the transplant showed strong positivity, probably reflecting the presence of passenger leukocytes from the donor. Subsequent peripheral blood samples were obtained at 2, 6, 9 and 12 months after the transplant, all being negative for the *JAK2* V617F mutation. Serial monitoring of peripheral blood counts showed initially mild thrombocytopenia which subsequently resolved. The blood counts remain normal 54 months after the transplant, without any hematological evidence of myeloproliferation. The patient takes acetylsalicylic acid 81 mg as the only antithrombotic agent. No episodes of thrombosis or evidence of MPN has occurred since transplantation.

Discussion

This and a previous report (7) describe successful transplantation using the liver from a donor with ET and a positive *JAK2* V617F mutation. Ours is the first report providing long term follow up on a recipient of a solid organ transplant from a *JAK2* V617F positive donor without molecular or hematological evidence of MPN transmission. Greater caution might be required with respect to donors with PV and *JAK2* V617F mutation where older recipients from lower down the list might be chosen so that the theoretical additional risk of a shorter life expectancy should an MPN develop might be offset by the potential gain of earlier transplantation. When considering a potential donor with an MPN diagnosis, other considerations must be made. The first is that patients bearing the *CALR* mutation may suffer from a more aggressive form of ET which would require additional caution if found in the donor (2). The second is that several agents are approved for the treatment of ET and PV, including hydroxyurea, anagrelide, and interferon and new treatments for ET are becoming available which would rescue patients in the unlikely event that the disease is transferred from the donor to an organ recipient. The *JAK2* inhibitor ruxolitinib is currently approved for the treatment of MF and PV. Other inhibitors are currently being evaluated in all three MPN including the *JAK2* inhibitors momelotinib, pacritinib and fedratinib, as well as the telomerase inhibitor imetelstat, which has induced rapid and durable hematologic and molecular responses in patients with ET (1,8,9). We believe that it is reasonable for organ procurement organizations to offer organs from donors with *JAK2* V617F mutations for transplantation into informed willing recipients within programs that provide appropriate follow-up, and in particular in situations in which the benefit from the transplant may supersede the potential and theoretical risk of MPN transmission.

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None.

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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