To the editor:

Correcting 2 more myths regarding transplants for AML in second remission

A recent Blood Perspective report by Forman and Rowe challenged the myth that in persons with acute myeloid leukemia (AML) in first remission, one can take a wait-and-see approach: if relapse occurs persons in second remission can undergo transplantation. The authors correctly suggest that few people with recurrent AML achieve second remission and are fit to proceed to a transplant. This leads them to conclude that transplants in persons with AML in first remission should be more often considered, especially persons with minimal residual disease (MRD) who may have an increased likelihood of relapse. What precisely MRD is and how it is defined are not specified, which is potentially problematic. Although we agree that second remissions are infrequent in persons who relapse, these data do not necessarily result in recommending transplants in first remission because it perpetuates 2 other myths: (1) that only persons who achieve a second remission benefit from a transplant and (2) that we can accurately predict at the subject level which persons with AML in first remission are likely to relapse.

Results of transplants in persons achieving second remission are clearly better than results of transplants in those who fail to achieve second remission but receive a transplant anyway. But this is a self-fulfilling prophecy based predominately on data from observational databases of transplant recipients rather than the entire relapse cohort including persons who could have received a transplant but did not. Moreover, some persons, albeit few, who relapse may achieve long-term survival or even cure with reinduction chemotherapy, especially those whose first remission was >18 months. Results of MRD testing in the only prospective study in persons with AML were informative regarding a transplant decision in <20% of the starting cohort.

Although most persons who relapse never achieve a second remission, many could receive a transplant without further therapy or with additional therapy aimed at disease control rather than remission reinduction. Importantly, there are no convincing data from prospective studies that giving antileukemia drugs to persons with AML who relapse and then proceed to a transplant improves outcomes. Data from a recent large clinical trial support this conclusion.

Much of the variance in the outcome of persons with AML in first remission remains unexplained. It follows that the best predictor of relapse is relapse. The only potential disadvantage of using relapse to trigger a transplant decision is if the outcome of transplants in relapsing persons is compromised by waiting for relapse in precisely the same subjects. This is not proved.

We appreciate Forman and Rowe’s thoughtful discussion of the myth of transplants in second remission but suggest current data are inconclusive as to whether to recommend transplants in persons with standard- or high-risk AML in first remission, even those with MRD. More importantly, we want to disarm 2 other myths: (1) that only those achieving second remission benefit from a transplant and (2) that we can, at the subject level, accurately predict which persons with AML in first remission will relapse. More data are needed on these complex issues.

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Acknowledgments: R.P.G. acknowledges support from the National Institute for Health Research Biomedical Research Centre funding scheme.


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References

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To the editor:

Association of a single-nucleotide polymorphism in the SH2B3 gene with JAK2V617F-positive myeloproliferative neoplasms

In a recent paper, Perez-Garcia et al described an inherited mutation in the SH2B3 gene associated with the development of acute lymphoblastic leukemia. SH2B3 encodes the lymphocyte adaptor protein (LNK) that negatively modulates the signaling of several cytokine receptors, including the thrombopoietin receptor (myeloproliferative leukemia virus oncogene [MPL]) and the erythropoietin...
Table 1. Frequency of SH2B3 c.784T>C in MPNs vs controls, MPNs JAK2V617F vs controls, MPNs JAK2V617F vs MPNs JAK2WT, and MF JAK2V617F vs controls

<table>
<thead>
<tr>
<th>Allele</th>
<th>MPNs (n = 317)</th>
<th>Controls* (n = 2851)</th>
<th>OR</th>
<th>95% CI</th>
<th>$\chi^2$ (df = 1)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Allele 784C</td>
<td>312 (49.2)</td>
<td>3201 (56.1)</td>
<td>1.00</td>
<td>(reference)</td>
<td></td>
<td></td>
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<tr>
<td>Allele 784T</td>
<td>322 (50.8)</td>
<td>2501 (43.9)</td>
<td>1.32</td>
<td>1.12-1.56</td>
<td>11.15</td>
<td>$8.0 \times 10^{-4}$</td>
</tr>
<tr>
<td>Allele JAK2V617F</td>
<td>159 (43.2)</td>
<td>3201 (56.1)</td>
<td>1.00</td>
<td>(reference)</td>
<td></td>
<td></td>
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<tr>
<td>Allele 784C</td>
<td>209 (56.8)</td>
<td>2501 (43.9)</td>
<td>1.68</td>
<td>1.36-2.08</td>
<td>23.47</td>
<td>$1.0 \times 10^{-4}$</td>
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<tr>
<td>Allele JAK2V617F</td>
<td>159 (43.2)</td>
<td>153 (57.5)</td>
<td>1.00</td>
<td>(reference)</td>
<td></td>
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<td>Allele 784C</td>
<td>209 (56.8)</td>
<td>113 (42.5)</td>
<td>1.78</td>
<td>1.29-2.45</td>
<td>12.65</td>
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<td>Allele MF JAK2V617F</td>
<td>59 (36.4)</td>
<td>3201 (56.1)</td>
<td>1.00</td>
<td>(reference)</td>
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<td>Allele 784C</td>
<td>103 (63.6)</td>
<td>2501 (43.9)</td>
<td>2.33</td>
<td>1.61-3.08</td>
<td>24.81</td>
<td>$1.0 \times 10^{-4}$</td>
</tr>
</tbody>
</table>

CI, confidence interval; df, degrees of freedom; MF, myelofibrosis; WT, wild-type.

*Alcina et al, 2010. 9

receptor, by attenuating JAK2 kinase activation. LNK was also shown to bind and regulate mutant signaling molecules found in myeloproliferative neoplasms (MPNs) like MPL-W515L and JAK2V617F through its SH2 domain and a novel site at its amino-terminal region. Lastly, several acquired $SH2B3$ mutations in the pleckstrin homology domain and NH2-terminal region of the protein were reported in MPNs. 4,6 Moreover a nonsynonymous single-nucleotide polymorphism (SNP), rs3184504 (p;R262W, c.784T>C), in exon 2 of the $SH2B3$ gene was reported to be associated with type 1 diabetes, 7 risk of coronary artery disease, thrombocytosis, 8 and celiac disease.

To explore a potential predisposing role of this $SH2B3$ SNP sequence in MPNs, we analyzed it in whole-blood DNA in a large cohort of MPN patients with and without the JAK2V617F mutation. In a control population of 2851 individuals the reported T- and C-allele frequencies were respectively 43.9% and 56.1%. Of note, similar figures were found in another control group of 1005 Russian subjects. 10

We therefore analyzed the frequency of each allele of the rs3184504 in 317 MPN patients, including 169 patients with essential thrombocytopenia (103 with the JAK2V617F mutation and 66 without) and 148 with myelofibrosis (81 with the JAK2V617F mutation and 67 without). We found that the T-allele frequency was significantly higher than reported in the control populations (Table 1) (odds ratio [OR] = 1.32; P = .0008). We then studied the T- and C-allele frequencies between JAK2V617F-positive and JAK2V617F-negative patients. There was no association between the T/T profile and the percentage of JAK2V617F. We found that the T allele was significantly more frequent in JAK2V617F-positive patients as compared with controls (OR = 1.68; P = .0001) and JAK2V617F-negative patients (OR 1.78; P = .0004), whereas no difference was found between JAK2V617F-negative MPN patients and the control group (OR = 0.95; P = .663). Interestingly, the higher frequency of the T allele was associated with the JAK2V617F myelofibrosis group (OR = 2.23; P = .0001).

In conclusion, these results reveal a significant association between the c.784T>C nonsynonymous polymorphism of LNK and JAK2V617F-positive MPNs, further supporting a role of the $SH2B3$ gene in the predisposition to hematologic malignancies. Functional studies are required to understand how the T risk allele may contribute to the development of MPNs. In particular, the charge reversal due to this nonsynonymous SNP on a surface-exposed residue in the pleckstrin homology domain of the molecule may affect its interactions with downstream signaling molecules.
To the editor:

Hepatitis E transmission by transfusion of Intercept blood system–treated plasma

Hepatitis E virus (HEV) is a small nonenveloped RNA virus usually transmitted by the enteric route, although transmission by blood transfusion has also been reported.1-3 HEV infection usually leads to benign acute hepatitis. It can sometimes be fulminant, particularly among pregnant women and patients with preexisting liver disease, or evolve to a chronic state, especially in immunosuppressed subjects.1,4 Pathogen reduction (PR) of blood products (BPs) has demonstrated its effectiveness with regard to a large number of pathogens.5,6 Among PR methods, the Intercept method combines a synthetic psoralene amotosalen HCl treatment with ultraviolet A (UVA) light illumination to block the replication of DNA and RNA.

We report 2 cases of HEV transmission by 2 units of Intercept-treated plasma originating from the same donor. The first patient is a 36-year-old man with chronic renal failure. He underwent a kidney transplantation, which was followed by acute humoral rejection and was treated by plasma exchanges from March/June 2012, during which 59 BPs were transfused. Liver cytolysis was observed since June 2012. The diagnosis of hepatitis E was reached in October 2012 with detectable HEV RNA and weakly reactive anti-HEV immunoglobulin M. As of June 2013, the patient remained viremic, and ribavirin was introduced. HEV RNA was undetectable on the day of transplantation, as well as on the graft donor, but was detected in apheresis donation leading to transfused Intercept-treated fresh frozen plasma (FFP). The second patient is a 61-year-old man who underwent a liver transplantation for alcoholic liver cirrhosis in August 2012. Hepatitis E infection was detected in February 2013 with detectable HEV RNA and negative HEV serology. As of April 2013, the patient remained viremic, and ribavirin was introduced. He had received 72 BPs; HEV RNA was undetectable on the day of transplantation and in the graft donor but was detected in apheresis donation leading to transfused Intercept-treated FFP. All other blood donations for these patients tested negative for HEV RNA (using cryopreserved plasma samples collected on donation day). Further investigations revealed that the incriminated FFPS resulted from the same apheresis donation that was amotosalen/UVA light treated before segmentation in 3 units. Two of the 3 units were transfused to the 2 patients described above; the third was transfused to a patient who died 2 days following transfusion. The 2 FFP recipients and the donor were infected by a genotype 3f strain presenting a strict homology on partial sequences of the open reading frame 1 (ORF1) and ORF2 regions as previously described (Figure 1).7 Such strain identity demonstrates that both amotosalen and UVA light-treated FFPS provided by a unique donor transmitted HEV to ≥2 transfusion recipients. The involved donor was a 32-year-old woman who did not reveal any factor that could suggest that she was infected by HEV during the period of donation.

Such novel HEV transmission through Intercept-treated FFP establishes resistance of HEV to Intercept PR technology. Nonenveloped viruses such as HEV are also known to be resistant to solvent/detergent treatment. In vitro, assessment has established that hepatitis A virus, a similar nonenveloped virus, as well as feline calcivirus, a model for HEV, are poorly sensitive to amotosalen/UVA light.5,6 Hepatitis E has recently emerged as a significant cause of transfusion-induced viral hepatitis. Generalizing HEV screening for all blood donations, or alternatively for a fraction of BPs to be transfused in high-risk patients, is being considered in France.

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