

Indeed, our study of prospective EBV monitoring was initiated because of a case similar to the one described by Wondergem et al. Our patient was a 32-year-old man with severe aplastic anemia who received horse antithymocyte globulin (ATG) with no response at 3 months and was then treated with rabbit antithymocyte globulin. Two weeks later, rapidly progressive massive lymphadenopathy developed in the neck, axillary, and mediastinal areas, requiring endotracheal intubation. Axillary lymph node biopsy revealed EBV lymphoproliferation, accompanied by an EBV viral load of 870 000 copies per  $10^6$  mononuclear cells in the blood. Cyclosporine was discontinued and the patient received one cycle of cyclophosphamide, doxorubicin, vincristine, prednisone plus rituximab (CHOP-R) with a rapid decrease in node size and in peripheral blood EBV copy numbers. He went on to unrelated hematopoietic stem cell transplantation for his aplastic anemia and 4 years later he is doing well with no further evidence of EBV disease.

Notwithstanding, EBV-lymphoproliferative disease after immunosuppression for aplastic anemia is very rare and its occurrences have been limited to case reports. We have now monitored EBV reactivations in more than 150 courses of immunosuppressive therapy with no additional cases of EBV disease, despite very high viral loads and

prolonged periods of EBV polymerase chain reaction (PCR) positivity. In the past 18 months we have monitored EBV viral loads in patients who received rabbit ATG as initial therapy; higher viral loads were again observed in patients treated with the rabbit ATG up-front (similar levels to what was reported in the manuscript when rabbit ATG was administered as a second course only) compared with those who received horse ATG. Therefore, the EBV viral load cannot be interpreted in isolation as cut-off values that are predictive or diagnostic of disease have not been established. Rather than mandate routine testing for what we believe is a rare event, we would instead prefer to stress awareness of the potential for EBV reactivation and disease, with intervention only when there is clinical suspicion due to rising lactate dehydrogenase (LDH), lymphadenopathy, clinical deterioration in association with a high EBV viral load, and confirmatory lymph-node histology.

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## To the editor:

### Physical and not mental health is impaired in very long-term survivors after HSCT compared with their respective donors: a paired analysis

Bhatia and colleagues<sup>1</sup> recently published a comprehensive analysis on late mortality after allogeneic hematopoietic stem cell transplantation (HSCT), providing interesting data about the functional status of 547 recipients and 319 siblings. At the time of this Collaborative Bone Marrow Transplant Survivor Study, patients and donors had a median age of 41.5 and 44 years, respectively, and a median time of 8.6 years after HSCT. By questionnaire, long-term survivors reported significantly more difficulties in integration back into society after HSCT, in holding down employment, or in obtaining or retaining health insurance compared with their siblings. These results provided additional information to the relatively scarce and partially conflicting reports on functional status in the long-term recipients of HSCT surviving more than 10 years.<sup>2,3</sup>

In order to obtain a comprehensive overview on physical and mental health in very long-term survivors after HSCT, we invited 44 recipients and their respective HLA-identical sibling donors to take part in a prospective study at the University Hospital of Basel. Both the recipients and their donors were controlled at the same time point, in pairs, and were given a complete clinical and biologic examination. Each answered a Short Form 36 (SF-36) Health Survey,<sup>4,5</sup> which provides the generic health status measure using 36 items assessing 8 different concepts (Table 1). Three of the concepts provide a score for physical health, 3 for mental health, and 2 for general health status. These 8 concepts are summarized in 2 global tests, one for physical and one for mental health. Norm-based scores were used, in which 50 represents the mean score, and 10 the standard deviation for the general population. The median age of the recipients and donors at time of the study was 44.3 years (24-63) and 43.4 years (22-61), respectively, with a median time of 17.5 years (range, 11-26 years) after HSCT. Four patients received an HSCT for aplastic anemia and 40 for hematologic malignancies. All patients received bone marrow as

stem cell source and total body irradiation was part of the conditioning in 39 patients (89%). Acute graft-versus-host disease (GVHD) was observed in 31 (70%), and chronic GVHD in 22 (50%) patients.

In a paired comparison, recipients showed a significantly lower rank of the norm-based scores for all questions related to physical well-being, except for role limitation, but no difference in the mental health scores compared with their respective donors (Table 1). This is confirmed by the global test for physical ( $P = .001$ ) and mental ( $P = .831$ ) health. Physical health was significantly lower in patients with extensive chronic GVHD ( $P = .05$ ), in females ( $P = .024$ ), in recipients older than 25 years at HSCT ( $P = .024$ ) or older than 42 years at study evaluation ( $P = .05$ ). None of these factors had an impact on mental

**Table 1. Short Form 36 Health Survey: Paired comparison between recipients and their respective donor**

Items	Donor*	Recipient*	P
<b>Items describing physical health</b>			
Physical functioning	54.7	50.9	.001
Role limitations due to physical health	54.6	52.3	.213
Bodily pain	59.2	54.9	.042
<b>Items describing general health (physical and mental)</b>			
General health perception	57.0	50.7	.001
Vitality	65.4	52.3	.039
<b>Items describing mental health</b>			
Social functioning	54.0	51.2	.324
Role limitations due to emotional problems	53.9	51.0	.285
Mental health	52.7	50.9	.638
<b>Global tests</b>			
Physical Component Summary (PCS)	57.1	52.8	.001
Mental Component Summary (MCS)	52.9	50.8	.831

\* Numbers are means of norm-based scores.

health status (MCS,  $P > .10$ ). In summary, our data extend the findings reported by Bhatia et al<sup>1</sup> on the functional health status in long-term survivors, validating the finding that the physical health status of very long-term survivors after HSCT can be impaired, while mental health status remains preserved.

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## To the editor:

### Revised criteria for the myeloproliferative disorders: too much too soon?

We would like to raise several concerns about the updated World Health Organization diagnostic criteria for polycythemia vera (PV), essential thrombocythemia (ET), and primary myelofibrosis (PMF), as proposed by Tefferi et al.<sup>1</sup>

First, while the authors explain that the new criteria are not absolutely comprehensive, they never state the exact purpose of this revision. As a purpose of diagnostic criteria is to guide diagnosis and clinical management, the authors should demonstrate that the revised criteria are validated by data from previous studies. For example, while the discovery of the *JAK2V617F* mutation is of paramount importance, it has not changed our ability to discriminate between the different disorders and has not changed therapeutic recommendations, although it may in the future. Without these supporting data, these criteria produce significant ambiguity for physicians attempting to decipher their clinical relevance.

Second, the new criteria emphasize differences in bone marrow morphology among the myeloproliferative disorders. But, it appears that the vast majority of this work has been done with small groups of patients in retrospective and unblinded settings, which may facilitate biases and misinterpretations. In addition, the references supporting these morphologic criteria primarily focus on the work of one of the authors. We have concerns about the general applicability of these guidelines to centers that lack the necessary hematopathology expertise. Is there sufficient confidence that evaluation of megakaryocyte morphology and fibrosis is widely reproducible among the various observers who will be attempting to make these distinctions? This concern is shared by others.<sup>2,3</sup> We also question whether morphologic assessment can reliably differentiate between primary and secondary causes of myelofibrosis, such as seen in primary pulmonary hypertension, a common cause of secondary myelofibrosis. Rather than stating that “the histologic differences among the entities outlined here are recognized by experienced hematopathologists,” the authors

should provide objective evidence of the validity, utility, consistency and reproducibility of the proposed criteria.

Third, the morphologic criteria have never been applied to patients with congenital polycythemia due to *Von Hippel-Lindau* or *EPO* receptor gene mutations. In our experience with these disorders, many of these patients had their marrow morphology interpreted as consistent with PV.<sup>4,5</sup>

In addition, there is a major mistake in Tefferi et al’s Table 1,<sup>1</sup> which summarizes the 2001 criteria; contrary to what is stated in the table, dominantly inherited polycythemia due to a truncated erythropoietin receptor is always associated with a low erythropoietin level.

In summary, we feel that before using the revised criteria as a diagnostic guide, these issues need to be further evaluated in large scale, prospective studies, such as those being undertaken by the Myeloproliferative Disorders Research Consortium.

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