molecular and hematologic analyses. As expected, Runx1bEx6e exhibited loss of transcriptional activity in a reporter assay but enhanced colony-forming capability compared with the FL isoform. Bone marrow transplantation assay using cells that have been retrovirally transduced with these isoforms also clearly demonstrated that the mice that were recipients of Runx1bEx6e-transduced cells revealed continuous increase in engraftment, but the recipients of Runx1bEx6e−transduced cells showed a decrease of transplanted cells. Runx1bEx6− also showed low engraftments, although this isoform behaved similarly to Runx1bEx6e in some assays.

The strongest evidence for the Runx1bEx6e-mediated HSC expansion came from the data of Runx1-IRES-GFP knockin (KI) mice, originally generated for other purposes. Fortunately for the authors, these KI mice lack the exon 6–related alternative splicing isoforms that include Runx1bEx6e, hence serving as the best platform to prove the in vivo functionality of the isoforms of interest. The KI mice had signiﬁcantly fewer c-Kit+ Sca1 lineage marker− cells, which include HSCs and multipotent progenitors, than control mice. In vivo competitive repopulation assays demonstrated a sevenfold difference of functional HSCs between wild-type and KI mice. On the basis of these results, the authors concluded that the Runx1bEx6e isoform functions as a counter player against the FL isoform. Runx1bEx6e regulates HSC pool size in a positive manner, whereas Runx1bEx6− does so negatively. The long-awaited positive regulator for HSC expansion in mice, equivalent to human RUNX1a, is now clearly shown to be Runx1bEx6e.

Fine-tuning of the balance between such positively and negatively regulating Runx1 isoforms is reported to work in hematopoietic commitment of embryonic stem cells and many other biological processes. Notably, imbalance of RUNX1 isoforms has been suspected to be an underlying mechanism for leukemogenesis. Recent advances in sequencing technology have unraveled a plethora of mutations in splicing factors (SFs) in human hematologic malignancies. The precise mechanisms by which these SF mutations cause diseases remain unknown. Deregulation of RUNX1 splicing machinery could be the key driving force of leukemia stem cells carrying SF mutation. Further investigations on splicing mechanism would provide us with deeper insights into both normal and pathological stem cell behaviors.

Conflict-of-interest disclosure: The author declares no competing financial interests.

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Comment on Geyer et al, page 3803

Symptom burden in hematologic malignancies

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In this issue of Blood, Geyer et al1 report results from a large multinational survey in which a sizeable proportion of patients with myeloproliferative neoplasms experienced severe symptom burden. However, standard measures of disease severity and risk did not always predict which patients would have high levels of symptom distress.

The availability of new agents to treat hematologic malignancies, including many with molecular and genetic targets, is producing better disease control and significantly extending survival.2 As a result, various hematologic cancers that before were rapidly fatal have become chronic conditions that can be managed with continued treatment.3 When treatment only marginally extended survival, life-threatening toxicities were the main concern in making decisions about the acceptability of therapy; today, with significantly prolonged survival, it is critical that we expand our view of the outcomes of therapy to include how patients feel and function during extended periods of treatment.

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Given that an increasing number of therapies have similar survival outcomes, documenting better functioning, reducing disease-related symptoms, and causing fewer treatment-related symptoms create a significant therapeutic advantage. Knowledge about the effects of a particular agent on symptomatic and functional status is helpful for both patients and their health care teams as they choose among treatments with similar standard clinical outcomes.

There has been a long tradition of evaluating treatments for metastatic solid tumors in terms of relative impact on health-related quality of life (HRQOL). For hematologic malignancies, however, less attention has been paid to eliciting the patient’s experience during treatment—perhaps because of the lethality of many of these cancers. One reason for the reluctance to include HRQOL measures in hematologic malignancy clinical trials is the additional costs and time commitments required of investigators and patients to administer and complete patient-reported questionnaires (measuring these toxicities via clinician ratings, a typical approach, does not optimally capture the patient experience during therapy). Also, many HRQOL questionnaire items address the patient’s perception of life domains that are less pertinent to the direct effects of the treatment and disease and therefore insensitive to changes during treatment. The most sensitive measures of response to therapy are usually the patient’s report of changes in symptoms as treatment progresses. These disease-related and treatment-specific symptoms are often referred to as symptom burden, as Geyer et al. note.

Symptoms and their impact on functioning are conceptually most proximal to the disease process and its alteration by treatment (see figure 6). If the symptoms most relevant to the disease and treatment being studied can be identified, patient ratings can be gathered in a few minutes via a short, targeted questionnaire, thus significantly reducing patient and investigator time and cost. These short questionnaires are highly compatible with electronic data capture, allowing more frequent assessment of symptoms from patients away from the clinic via computer-assisted telephone assessments, Web applications, and smartphones. Frequent data collection during a trial can answer questions about when patients can expect treatment-related symptom burden and disease-related symptom relief.

Identification of the symptoms most appropriate for evaluation of a particular agent in a particular malignancy is a complex process, and complete consensus about how this should be done is lacking. One approach is that used to develop the Myeloproliferative Neoplasm Symptom Assessment Form (MPN-SAF). MPN-SAF symptom items were selected from those most endorsed by an international sample of patients with myeloproliferative neoplasms. The final MPN-SAF used by Geyer et al.1 includes 10 symptoms most representative of myeloproliferative neoplasms, scored on a 0 (absent) to 10 (worst imaginable) scale. In a recent clinical trial of ruxolitinib, a Janus kinase inhibitor, in patients with myelofibrosis, the MPN-SAF documented substantial rapid improvement in several symptoms, including fatigue, weight loss, night sweats, and pruritus, and in daily functioning. This proof of clinical benefit led to inclusion of symptom reduction in the Food and Drug Administration labeling indications for ruxolitinib for the treatment of myelofibrosis, evidencing the important contribution that symptom assessment can have in hematologic malignancy clinical trials.

Within the drug development and evaluation process, the systematic administration of symptom measures at frequent intervals in early-phase clinical trials can supply critical information about treatment toxicities or symptomatic benefits, such as reduction of disease-related symptoms and improved function. Qualitative interviews with patients can verify that salient symptoms are being assessed and capture additional treatment-related symptoms that should be added to routine assessment. Even though these trials may enroll fewer than 100 patients, early evidence of multiple treatment-related toxicities can serve as a warning that adherence to treatment may be compromised and that the appropriateness of dose selection or plans for supportive care may need to be reconsidered.

The Eastern Cooperative Oncology Group conducted the nationwide Symptom Outcomes and Practice Patterns (SOAPP) study (www.ecogsoapp.org) to create a database that includes symptoms reported by >3,000 patients with breast, lung, prostate, or colorectal cancer using the MD Anderson Symptom Inventory, a brief, concise multisymptom assessment questionnaire. With the work of Geyer et al., such a database now exists for myelofibrosis patients. A similar database for hematologic malignancies would be highly valuable. Baseline data on symptoms for standard treatments can be extremely useful in planning and evaluating clinical trial outcomes for new therapies. Applying various methods of symptom clustering, one of which was used by Geyer et al., may help in developing hypotheses about the pathophysiology of symptoms. These data will also identify areas of need for symptom management to improve functioning and increase treatment tolerability for patients with hematologic malignancies.

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