Unexpectedly, and unlike in adult CXCR4 conditionally deleted mice, the increased hyperproliferation under SDF-1 deficiency provided the mice with the advantage of improved recovery and increased survival after 5-FU-inflicted myeloablative stress. This can be explained by the fact that these mice maintain an expanded pool of proliferating HSPC with increased differentiation potential which can replenish the mature white blood cells (WBC) pool as evident by higher WBC counts and increased BM cellularity 7 and 14 days after 5-FU treatment (see figure).

Because SDF-1 is presented mainly by the mesenchymal stromal compartment in the BM, the authors hypothesized that the observed hematopoietic phenotypes are driven by the SDF-1–deficient stromal cells. To segregate between these 2 compartments and to study how the SDF-1–lacking stromal microenvironment influences hematopoiesis, in vitro cocultures and in vivo chimeric mice were established. These models proved that in the absence of SDF-1, the stromal compartment fails to maintain LTR-HSC in vitro and facilitates in vivo a hyperproliferative state of cells transplanted from wild-type (WT) mice. Importantly, stromal–expressed cytokines which regulate HSC such as stem cell factor (SCF) are reduced in the absence of SDF-1. The decreased levels of SCF in SDF-1–deleted mice may explain the observed failure to maintain LTR-HSC during HSPC hyperproliferation, as these mice exhibit a phenotype similar to c-Kit (SCF receptor) deficient mice. It may also explain the preferential post–5-FU recovery of the more committed progenitors and mature WBC at the expense of LTR-HSC. Yet, this aspect still needs further investigation to reveal how the stromal microenvironment itself is influenced by the lack of SDF-1, as it was previously shown that both murine and human BM stromal cells functionally express CXCR4.2,7 Previous studies established that SLAM cells (representing LTR-HSC) interact with BM reticular adventitial cells expressing high levels of CXCL12 (CAR cells).6 More recently, a subset of these cells, positive for the neurofilament Nestin and expressing the highest levels of SDF-1, were identified as mesenchymal stem cells (MSCs), regulating HSC homing and maintenance.8 Applying conditional deletion of the SDF-1 allele from different HSC-supportive stromal cell types will reveal the roles of this ligand in regulation of HSCs, MSCs, and various stromal cell types in the BM and spleen (see figure).

Tzeng and colleagues also observed that in the absence of SDF-1, there is a significant topographic change in the BM in terms of localization of hematopoietic sites. During steady-state conditions, in the absence of SDF-1, HSPCs were not detected alongside the endostemum region, the border between the bone and the BM which contains high levels of SDF-1 presented by immature bone-lining osteoblasts.2,7 In addition, after 5-FU treatment, hematopoietic recovery was restricted only to the perivascular regions suggesting impaired function of the endosteal niches (see figure). Although the bone phenotype and endosteal topography require further investigations, these findings are fascinating considering the parallel study performed by the authors with regard to lung function in the absence of SDF-1.9 The same SDF-1–conditionally deleted mice exhibit a lung phenotype of increased alveolar air space and vessel hyperplasia accompanied with increased levels of phosphorylated endothelial nitric oxide synthase (eNOS). This observation raises the possibility of an indirect effect on hematopoiesis via eNOS activity. eNOS was shown to support HSPC development and proliferation.10 If eNOS is also up-regulated in BM and spleen vessels upon SDF-1 deletion, it may create an HSPC-preferable microenvironment, which may be the reason for the observed aberrant HSPC localization and hyperproliferation.

The article by Tzeng et al advances the field of hematopoiesis by allowing, for the first time, study of HSCs in their microenvironment under in vivo physiologic conditions in which SDF-1 is deleted during adulthood. The study reveals the importance of SDF-1 not only as a pivotal HSC chemoattractant,2,7 but also as the keeper of HSC quiescence, HSPC pool size, and proper niche functionality in the BM and spleen.

**Conflict-of-interest disclosure:** The authors declare no competing financial interests.

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**If Nostradamus were treated for MDS**

**Mikael A. Sekeres**  
**CLEVELAND CLINIC TAUSSG CANCER INSTITUTE**

The International Prognostic Scoring System (IPSS)1 and World Health Organization Prognostic Scoring System (WPSS)2 are great tools to distinguish lower- from higher-risk myelodysplastic syndromes in untreated de novo patients, accurately predicting survival and leukemia evolution. But what system would you use to advise a patient embarking on disease-modifying therapy?

The hypomethylating drug azacitidine was the first agent approved (in 2004) by the US Food and Drug Administration specifically for the treatment of myelodysplastic syndromes (MDS).3 Its US label includes all MDS subtypes, and approval was based in part on a combined endpoint of a significant delay in time to transformation to acute myeloid leukemia and death, compared with best supportive care, in a phase 3 Cancer and Leukemia Group B trial.3

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**Comment on Itzykson et al, page 403**

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Subsequently, in a phase 3 European study, azaci
tidine significantly improved overall survival in
higher-risk MDS patients when compared with con
ventional care regimens, with a median sur
vival of 24.5 months versus 15 months, respec
tively (hazard ratio, 0.58, P = .0001).4 The improved
outcomes were probably due to more narrowly
defining the MDS population in whom azaci
tidine is thought to have more activity (hy
permethylation with consequent gene inactivation is
more prevalent in higher-risk MDS, compared with
lower-risk subtypes)6 and to preventing
crossover from nonresponding control arm pa
tients to the azacitidine arm, as was allowed in the
Cancer and Leukemia Group B study. Patients
with higher-risk MDS comprise approximately
25% of newly diagnosed, and 15%-20% of es
established cases.6 It is difficult to determine which
of these patients is more likely to respond toaza
citidine and live longer as a result.

In this issue of Blood, Itzykson and col
leagues report the results from an analysis of
282 higher-risk MDS patients treated with
azacitidine in a compassionate use program in
42 centers in France.7 As opposed to patients
enrolled on many clinical trials, this is a re
sentative MDS patient group, with 22% hav
ing refractory anemia with excess blasts in
transformation/acute myeloid leukemia; 26%
with secondary MDS; 10% having been previ
ously treated with cytarabine; and 32% with
an erythrophoeisis-stimulating agent. Patients re
ceived a median of 6 cycles of therapy, and 17%
achieved a complete or partial response with an
additional 21% achieving hematologic improve
ment, according to 2006 International Working
Group response criteria8 and similar to the Euro
pean survival study. In addition, the investiga
tors verified the finding from the survival study that
patients achieving a hematologic improve
ment or better response lived longer.

In multivariate analyses, previous treat
ment with cytarabine, bone marrow blasts
more than 15%, and abnormal karyotype were
associated with a lower response rate, while
complex cytogenetics was associated with a
shorter response duration. Median overall
survival was 13.5 months, and again in multi
variate analyses, higher performance status
(Eastern Cooperative Oncology Group score ≥ 2),
intermediate and high-risk IPSS cyto
genetic risk categories, presence of circulating
blasts, and high red blood cell transfusion
needs (≥ 4 U/8 weeks) were associated
with worse survival. From these 4 variables,
a simple scoring system was developed, with
each given a value of 1 point (and 1 for inter
mediate, and 2 for poor-risk cytogenetics), and
patients were assigned to 3 risk categories (see
table): low (score = 0, median survival not
reached), intermediate (score = 1-3, median
survival 15 months), and high (score = 4-5,
median survival 6.1 months).

Although it is easy to use statistical tests to
identify factors associated with worse out
comes in any study, and by chance alone a factor
can be isolated if 20 are explored,
what makes this analysis special was valida
tion of these factors in a separate cohort of
patients treated with azacitidine—those
enrolled in the European azacitidine sur
vival study. In this population, the prognos
tic scoring system continued to accurately
distinguish survival among risk groups, with
median survival not reached for low risk,
21.4 months for intermediate risk, and
9.3 months for high-risk categories.
As would be expected in a clinical trial with
restrictive inclusion criteria, survival was
higher for each risk category compared with
survival in the compassionate use program.

So, how should the azacitidine-specific pro
gnostic scoring system be used in context of
broader MDS prognostic scoring systems, such
as the IPSS4 and WPSS? These nonspecific
MDS prognostic systems were developed based
on clinical and pathologic data from largely un
treated MDS patients—92% of patients in
cluded in the IPSS had received no therapy,
100% in the WPSS—and it would be the rare
patient included in one of these systems who
received disease-modifying therapy subsequent
to inclusion. That being said, the IPSS and
WPSS are useful in determining whether a pa
ient is considered higher risk at baseline, and
thus more appropriate to receive therapy with a
hypomethylating agent such as azacitidine.
At that point, the Azacitidine Prognostic Scoring
System can be invoked, to identify the group of
patients who would be predicted to have favor
able survival on azacitidine therapy, and those
with comparatively poor survival, in whom alter
native therapeutic strategies should be selected.
It will be exciting to see how this prognostic
schema compares to another schema used in
-treated patients, developed by the M. D. And
son group, and whether it can next be validated
in combination regimens that include azacitidine
and either a histone deacetylase inhibitor or lenalido
dide.

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new risk model in myelodysplastic syndrome that accounts
for events not considered in the original International Prog

Table 1. Azacitidine Prognostic Scoring System

<table>
<thead>
<tr>
<th>Calculation of prognostic score</th>
<th>Scoring system parameters</th>
</tr>
</thead>
<tbody>
<tr>
<td>Score</td>
<td>0</td>
</tr>
<tr>
<td>Performance status</td>
<td>low</td>
</tr>
<tr>
<td>circulating blasts</td>
<td>None</td>
</tr>
<tr>
<td>red blood cell transfusions</td>
<td>&lt; 4 U/8 wk</td>
</tr>
<tr>
<td>IPSS cytogenetic risk group</td>
<td>Good</td>
</tr>
</tbody>
</table>

Estimation of prognosis

<table>
<thead>
<tr>
<th>Overall score</th>
<th>0</th>
<th>1-3</th>
<th>4-5</th>
</tr>
</thead>
<tbody>
<tr>
<td>APSS group</td>
<td>Low</td>
<td>Intermediate</td>
<td>High</td>
</tr>
<tr>
<td>Median survival, mo</td>
<td>Not reached</td>
<td>15 mo</td>
<td>6 mo</td>
</tr>
</tbody>
</table>

IPSS indicates International Prognostic Scoring System; U, units; and APSS, Azacitidine Prognostic Scoring System.
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Mikkael A. Sekeres