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cGVHD of skin: simple tools, great advances

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In this issue of Blood, Jacobsohn et al report that 2 simple and reproducible assessment tools, the National Institutes of Health (NIH) composite skin score and the Lee skin symptom scale, are powerful predictors of severity and prognosis of skin GVHD.1

Allogeneic transplantation was established as a curative procedure for hematologic malignancies in the early 1970s. Soon thereafter, a novel syndrome of chronic GVHD (cGVHD) was described with pleotropic clinical manifestations, multiple organ involvement, and a special predilection for the skin.2 From its earliest descriptions it was determined that cGVHD was a disease with a high fatality rate and that it frequently affected patients’ quality of life. Based on detailed analysis of 20 patients, limited and extensive cGVHD were proposed.3 Extensive cGVHD diminished function, quality of life, and life expectancy. But others found an inverse correlation between the occurrence of cGVHD and risk for disease recurrence in leukemia.4 Ever since, observations have been reported associating mild cGVHD with improved long-term survival, while severe cGVHD is almost invariably associated with worse outcomes. Forty years later, definitions and classifications of cGVHD have been revised, but its management remains disappointing.5 First-line treatment relies on steroids or steroids with calcineurin inhibitors.6 More aggressive interventions such as the addition of

**Figure 1a: NIH composite skin score and relation to survival**

<table>
<thead>
<tr>
<th>Score definition</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
</tr>
</thead>
<tbody>
<tr>
<td>No symptoms</td>
<td></td>
<td></td>
<td>19%-50% BSA OR Deep sclerotic features “hidebound” (unable to pinch) OR impaired mobility, ulceration or severe pruritus</td>
<td></td>
</tr>
<tr>
<td>&lt; 18% BSA with disease signs but NO sclerotic feature</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Two-year overall survival

<table>
<thead>
<tr>
<th>Two-year overall survival</th>
<th>86%</th>
<th>83%</th>
<th>81%</th>
<th>69%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Two-year nonrelapse mortality</td>
<td>10%</td>
<td>13%</td>
<td>15%</td>
<td>30%</td>
</tr>
</tbody>
</table>

**Figure 1b: Calculation of Lee skin symptom scale: If all items are completed, total score is the sum of the points multiplied by 5**

<table>
<thead>
<tr>
<th>Abnormal skin color</th>
<th>Not at all</th>
<th>Slightly</th>
<th>Moderately</th>
<th>Quite a bit</th>
<th>Extremely</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rashes</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>Thickened skin</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>Sores on skin</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>Itchy skin</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
</tbody>
</table>

“We Please indicate how much you have been bothered by the following problems in the past month.”
mycophenolate mofetil do not improve long-term survival. What constitutes effective second-line treatment also remains to be determined. The results of promising phase 2 treatments have not often been confirmed in phase 3 treatments. Extracorporeal photopheresis, although widely considered beneficial and used frequently for advanced skin GVHD, did not achieve its primary end point when tested in a randomized study. Progress has been hindered by our limited understanding of the biology of cGVHD. But equally important is the lack of robust, reproducible, and validated methods for assessing the severity of cGVHD and its response to treatment. Several instruments—some of considerable complexity—have been proposed for assessment of skin GVHD, the most frequent target organ. Now, Jacobsohn et al report a prospective multicenter validation of these tools. For this purpose they followed 458 transplant patients and assessed severity of skin GVHD with various instruments. They compared the results of the instrument-generated scores with physician and patient assessment of improvement over time.

Assessment of the extent and severity of skin involvement using the NIH composite skin score (see figure panel A) correlated well with severity of symptoms. By contrast, more complicated assessments correlated poorly with patient or physician perception. The same NIH composite skin score also correlated with survival. Worsening in NIH skin score at 6 months was associated with higher mortality and higher nonrelapse mortality compared with stable NIH skin score. The latter observation suggests that the NIH composite skin score could serve as a short-term surrogate end point that predicts for long-term success or failure of novel drug therapies.

Another straightforward assessment tool completed by patients, the skin subscale of the Lee symptom scale (see figure panel B) also correlated well with physician and patient perception of improvement in cGVHD. A skin score of more than 15 correlated with worse survival, whereas improvement on the symptom scale was associated with improvement in survival.

This work provides validation of the proposals of the 2005 Chronic GVHD Consensus conference, and generates robust and reproducible tools that can be used for the assessment of novel therapies. A better delineation of risk categories of skin GVHD also constitutes a pivotal step toward generating better understanding of the disease biology.

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

REFERENCES

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Keep up the heat on IL-1

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In this issue of Blood, Capitano et al report an unexpected but clinically relevant finding that mild heating of mice enhances the postradiation recovery of neutrophils via an IL-1, IL-17, and G-CSF mechanism. Interleukin-1 is a master cytokine regulating inflammatory and immune responses. But there are two faces to the biology of IL-1: IL-1 can be causative in the manifestations of a broad spectrum of diseases, but IL-1 can also provide the host with protective mechanisms required to fight infection. For example, IL-1 stimulates hematopoiesis, particularly for neutrophils. Indeed, IL-1 was given to patients to shorten the nadir of bone-marrow suppression after chemotherapy. New data suggest that this latter property of IL-1 is enhanced at elevated temperatures during in vivo mouse models of neutrophil recovery from radiation. This observation is consistent with what we know about IL-1.

Early research on IL-1 was carried out to isolate the endogenous fever—producing protein then called leukocytic pyrogen (reviewed in Dinarello). Indeed, recombinant IL-1 (either IL-1α or IL-1β) is the most potent pyrogen for humans, producing fever at doses as low as 1 ng/kg (reviewed in Dinarello). Human responses to IL-1 also target the hematopoietic system as IL-1 induces neutrophilia via induction of G-CSF. In fact, fever and neutrophilia are the two most consistent clinical findings in patients with autoinflammatory diseases; on IL-1 blocking monotherapy, both are promptly brought under control. Therefore, during infections, elevated body temperature (fever) may affect immunologic responses to the infectious agent. Several reports showed that immunologically active cytokines such as IL-2 result in greater in vitro responses at 39°C compared with 37°C.

If elevated temperature augments immune responses, some asked whether elevated body temperature would affect the hematopoietic system. Capitano and coworkers have identified a unique mechanism that allows for a more rapid return of peripheral neutrophil after total body radiation. They demonstrate that mild elevation in body temperature (39.5°C) in mice that had been subjected to total body irradiation did in fact increase the recovery from neutropenia secondary to the radiation. Hematopoietic stem cells and neutrophil progenitors were elevated by a mild increase in temperature and these increases were reflected in the total circulating neutrophils regardless of mouse strain. Most interestingly, these increases are apparently due to a cascade of cytokines in that IL-1 induces IL-17 and IL-17 induces G-CSF.
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