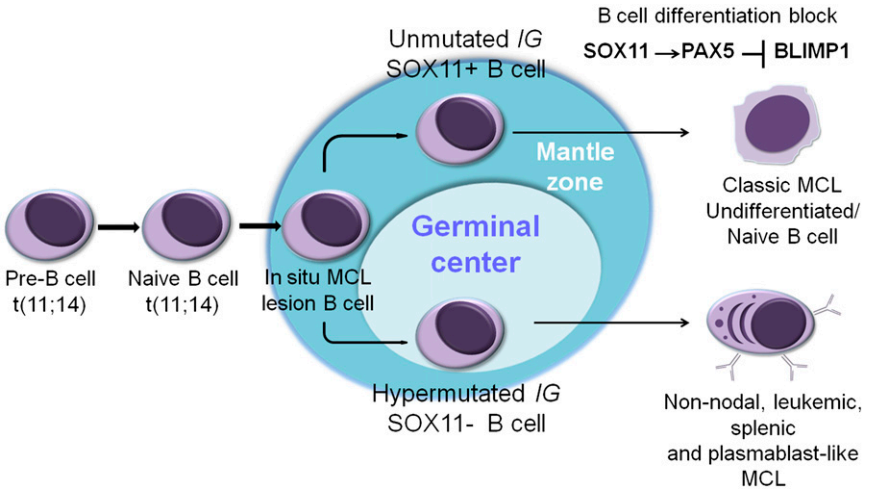

Hypothetical models of SOX11-possitive vs SOX11-negative MCL. The naive B cell carrying the t(11;14) colonizes the mantle zone of the lymphoid follicle and generates an in situ MCL lesion. Most MCLs evolve from these cells in the marginal zone with no or limited *IGHV* somatic mutations and SOX11 expression. SOX11 overexpression in conventional MCL may block the cells in a mature B-cell stage, preventing their further differentiation thought the SOX11-PAX5-PRDM1/BLIMP regulatory axis. Alternatively, some cells with the t(11;14) may enter the germinal center, undergo *IGHV* somatic hypermutation, and lack expression of SOX11. SOX11 may modulate the mature B-cell and early plasma cell differentiation program in MCL.

enrichment of SOX11 upregulated genes in SOX11-positive tumors and SOX11 downregulated transcripts in SOX11-negative lymphomas, respectively. Consistently, SOX11-positive MCL signatures were enriched in B-cell vs plasmablast and PAX5 activated gene sets, whereas the SOX11-negative MCL program was characteristically enriched in plasmablast-associated transcripts. Moreover, histologic and flow cytometry examination showed signs of focal plasmacytic differentiation and downregulation of B-cell marker expression in SOX11-negative tumors.

Overall, these results demonstrate an essential role for SOX11 in the growth of MCLs in vivo and support a role for the SOX11-PAX5-PRDM1/BLIMP1 regulatory axis in the maintenance of B-cell features and suppression of plasma cell differentiation programs in MCL. Still, several questions remain to be elucidated: What drives the aberrant expression of SOX11 in MCL? What are the specific mechanisms mediating the antilymphoma effects of SOX11 inactivation observed in mouse tumor xenografts? Is there a physiologic counterpart of the MCL-associated SOX11-PAX5-PRDM1/BLIMP1 regulatory axis in normal B cells? If so, what are the SOX factors upstream of PAX5-PRDM1/BLIMP1 in B-cell development?

The studies by Vegliante et al highlight the power of integrative analyses coupling carefully crafted mechanistic studies, genomic analyses, and expert histopathologic examination of clinical samples to uncover basic mechanisms underlying the biology of MCL.

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

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● ● ● TRANSPLANTATION

Comment on Inamoto et al, page 2340

Order out of chaos

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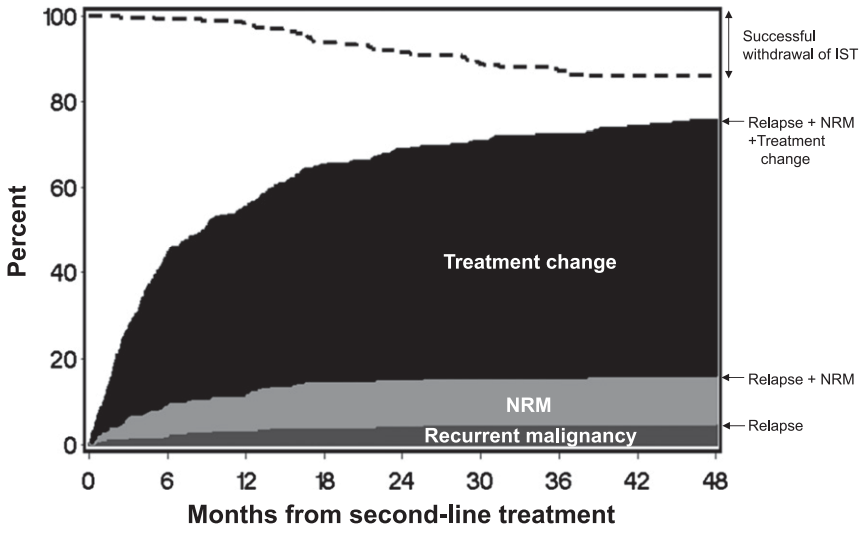
In all chaos there is a cosmos, in all disorder a secret order. (Carl Jung)

In this issue of *Blood*, Inamoto et al show that chronic graft-versus-host disease (cGVHD) has emerged from the chaos as a distinct disease with validated staging and response criteria. Inomata et al also show that there is order in steroid refractory cGVHD that can be exploited to better design and interpret therapeutic trials.[1]

Basic and clinical interest in chronic graft-versus-host disease (cGVHD) has exploded since the publication of the National Institutes of Health (NIH) Consensus Criteria for cGVHD in 2005-2006 (summarized in Pavletic et al[2]). Why this explosion? Quite simply, communication. Instead of each investigator living in his or her own parallel universe and having no effective way of communicating the extent of disease or the response to treatment, investigators now have a common language they can use to work with each other. Admittedly, much of the initial published work has been in validating and refining the NIH criteria.[3,4] But, as demonstrated by the Inamoto et al article, the order necessary for true basic and clinical advances is becoming evident.



Relapse	3%	4%	4%	5%	5%	5%	5%	5%
NRM	7%	9%	11%	11%	11%	11%	11%	11%
Treatment change	34%	43%	50%	53%	55%	57%	58%	59%
FFS	56%	45%	35%	31%	29%	28%	26%	25%
Withdrawal of IST	1%	2%	6%	8%	11%	13%	14%	15%

Failure-free survival after second-line treatment of chronic GVHD (from Inamoto et al). The black area represents treatment failure due to onset of third-line systemic treatment, the dark gray area represents treatment failure due to recurrent malignancy, the light gray area represents treatment failure due to nonrelapse mortality (NRM), and the white area represents failure-free survival (FFS). The dashed line represents cumulative incidence of successful withdrawal of all systemic immunosuppressive treatment (IST) during second-line treatment. See Figure 1 in the article by Inomata et al that begins on page 2340.

Inamoto et al report a retrospective study of 312 patients who received second-line systemic treatment for cGVHD to characterize causes of treatment failure, to identify prognostic factors associated with treatment failure, and to develop shorter-term end points for trials that test second-line systemic treatment of cGVHD.[1] The primary end point was failure-free survival, defined by the absence of third-line treatment, nonrelapse mortality, and recurrent malignancy during second-line treatment. Treatment change was the overwhelming cause of treatment failure, as shown in the figure. By 6 months, 34% of patients were on third-line treatment, and an additional 10% died or had relapsed. Multivariate analysis showed two expected (lower gastrointestinal involvement at second-line treatment and severe NIH global score) and one unexpected (high-risk disease at transplantation) risk factors for treatment failure. These three factors were used to define risk groups, and success rates at 6 months were calculated for each risk group (without or with various steroid dose limits).

Many have been frustrated by the lack of reproducibility of trial results in steroid refractory cGVHD. This same group of investigators has championed the premise that the problem is due to lack rigor in study design; it is hard to interpret, compare, or reproduce studies without clarity in the study design and assumptions.[5] The current study suggests that at least some of the splay in results may be due to the risk factors of patients enrolled in the initial vs subsequent confirmatory studies. Although most would have predicted that those with severe involvement of multiple organs and possibly lower gastrointestinal involvement would have a worse treatment outcome, few would have considered the underlying disease indication for transplant as a risk factor or that response to treatment based on these three risk factors could be grouped in the manner demonstrated here. It would be intriguing to reexamine the results of steroid refractory cGVHD trials in this light. However, most steroid refractory cGVHD trials were not limited to second-line treatment, and multiple studies have suggested that responses were less common in heavily pretreated patients. Hopefully, Inamoto and his collaborators will extend this study to look at those who did require third-line and beyond lines of treatment and to look at those patients with "stable" disease. The tempo of response needs to be better defined in order to better understand when stable truly indicates failure.

The one significant caution with the data presented in this article is that "lack of improvement after at least 2 weeks of initial treatment" may be too small a window to declare a treatment failure, especially in patients with sclerotic skin changes.

The investigators also propose that the combination of steroid dose (which correlated with the subsequent withdrawal of immunosuppressive treatment) and failure-free survival rates at 6 months could be used as the basis for a clinically relevant and efficient shorter-term end point in studies evaluating second-line systemic treatment of cGVHD. The protracted time needed to conduct cGVHD trials has been a substantial obstacle to progress in clinical care of this disorder. Neither drug companies nor junior investigators trying to establish their careers are interested in trials requiring 5 to 10 years to complete. Patients deserve better than an educated guess as to their best option for treatment, especially given that half will be placed on second-line treatment within 1 year of diagnosis.[6,7] Although enrolled patients would continue to need to be followed, these data suggest that a 6-month end point should give a good indication of the promise (or lack or promise) of the second-line treatment.

There has been a similar, but more modest, explosion in the basic science investigation of cGVHD. It is still hard to see order in the data, but at some point soon, the bigger picture of the pathophysiologic mechanism producing cGVHD will become clearer. As recently summarized by Paczesny, biomarkers for cGVHD should be pursued and will help drive this understanding.[8] When these become available, the synergy of clinical and laboratory end points should allow for even more rapid clinical evaluation of new and better options for first-line and subsequent treatment. Because it is likely that multiple immunologic pathways are involved, it will also allow patients to receive more targeted treatment. The study by Inamoto et al should bring us all closer to the secret order of cGVHD, a day that will be celebrated by transplantation centers and patients alike.

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

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