the rates of severe toxicities in high-risk patients. Moreover, identifying “low-risk” patients who may be safely treated as outpatients is important. Studies examining late toxicities such as prolonged myelosuppression have been largely limited to single-institution experiences. To that end, we support the blueprint set forth by the American Society of Hematology (ASH) task force on immunotherapies, which advocates for real-time data sharing and a centralized biobank. Multi-institutional collaborations using “real-world” data as reported in this study are critical for advancing the field and increasing the use of CAR T-cell therapy outside of highly specialized academic centers.

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REFERENCES

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Comment on Meier-Abt et al, page 2514

Complex systems analysis by integrative omics

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In medicine, the unraveling of etiologies, risk factors, disease mechanisms, and genotypes/phenotypes is essential for effective therapy, particularly for complex disorders. In this issue of Blood, Meier-Abt et al report a complex systems analysis of chronic lymphocytic leukemia (CLL) using an integrative OMICS approach together with ex vivo drug response and clinical outcome data. Using this multidimensional approach, they obtained both confirmatory and novel data that offer many opportunities for further elucidation and/or investigation to improve the therapeutic outcome of CLL.

All elements (eg, DNAs, RNAs, proteins, lipids, metabolites) of a cell play an important role in maintaining homeostasis, whereas imbalances or defects in these elements may cause diseases. Large-scale analysis of single elements (ie, genomics, transcriptomics, proteomics, lipidomics, and metabolomics) is useful for addressing disease mechanisms and defining novel biomarkers. However, it cannot capture the interplay of these factors to present a complete picture of a complex disease such as CLL. This underscores the need for more robust analyses using an integrative approach (ie, integrative omics).

Meier-Abt et al used unbiased data-independent acquisition mass spectrometry (in which ions of all peptides within a mass range, not only the predefined or preselected ones, are fragmented and further analyzed) using 2 different mass spectrometric modalities ( Orbitrap Fusion Lumos and timsTOF) for proteomics analysis of 117 CLL patients’ mononuclear cells and CD19+, CDS+, and light chain restricted malignant B cells. Integrating the obtained proteomics data with the available transcriptomics, genomics, ex vivo drug response, and clinical outcome data, analyses were then performed using bioinformatic tools and statistical packages to determine associations between/within parameters or elements.

This complex systems analysis has revealed that CLL with trisomy 12, immunoglobulin heavy-chain variable region gene mutational status, mutated SF3B1, trisomy 19, del(17)(p13), del(11)(q22.3), mutated DDX3X, and/or mutated MED12 is associated with differentially expressed proteins as compared with CLL without each of these factors. Correlation analysis of protein-RNA expression of the affected genes on chromosome 12 in patients with or without trisomy 12 has demonstrated coordinated, uncoordinated, and contradictory changes of protein and RNA expression (see figure). It is not surprising that the correlation between alterations in protein abundance and changes of RNA expression is relatively low (median coefficient of correlation is only 0.18), suggesting that a variety of protein forms/fragments and posttranslational modifications, which commonly occur in cancers, should not be overlooked. If these are considered during analyses, there may be more clues of a protein-RNA relationship. Multi-dimensional association study has shown that trisomy 12 and immunoglobulin heavy-chain variable region gene mutational status are the most prominent disease drivers via phosphoinositide 3-kinase (PI3K), a serine/threonine protein kinase (AKT), mammalian target of rapamycin (MTOR) signaling and STAT2-JAK1-PTPN6-CD79A-PTPN11-PIK3CD interacting complex (or interactome). In addition, protein arginine methyltransferase 5, pescadillo ribosomal biogenesis factor 1, and glycogen phosphorylase B
can predict the clinical outcome as shown by time to next treatment. In ex vivo drug response profiles, cobimetinib is associated with the greatest number of differentially expressed proteins, especially STAT2. Interestingly, high STAT2 expression is associated with activation of the interferon pathway and upregulation of NUP107, LEMD3, IFI44, and IFI44L1, which are downregulated in the STAT2-knockout CLL cells. From the many differentially expressed proteins identified, only STAT2 has been validated for its functional relevance in disease pathway. Therefore, more target proteins should be further explored for their impact on the pathogenic mechanisms of CLL.

Multiple element analysis (ie, combined genomics, epigenomics, and transcriptomics) has previously been used for investigation of their relationship with ex vivo drug response and clinical outcome data in CLL by the same network of investigators. The study by Meier-Abt et al, however, has expanded the dimensions of the complex systems analysis by integrating proteomics with more extensive analyses of the associations with genomics, transcriptomics, ex vivo drug response and clinical outcome data. The authors are to be commended for their efforts, especially in the robustness of the OMICS data, the cross-validation capability of the methods used, and the data sharing.

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REFERENCES
Comment on Najidh et al, page 2539

Blood will tell: profiling Sézary syndrome

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Sézary syndrome is a rare, aggressive leukemic variant of primary cutaneous T-cell lymphomas characterized by erythroderma (>80% body surface involvement), generalized lymphadenopathy, and circulating atypical lymphocytes called Sézary cells. Even though the circulating tumor clones are easily accessible for immunophenotyping in the blood, unequivocal identification and quantification of Sézary cells can be a challenge. Marker panels may fail to identify these cells, and there is considerable patient-to-patient variability. In the article by Najidh et al, blood cells from patients with Sézary syndrome were prospectively analyzed by both flow cytometric and RNA sequencing methods, which represent a highly sensitive and standardized approach based on the previously validated multiparameter EuroFlow marker panels. The authors demonstrate that conventional flow cytometry, generally used in clinical practice, either over- or underestimates the overall tumor burden when compared with EuroFlow. This finding adds a new aspect to the longstanding debate regarding whether percentages or absolute counts of circulating tumor cells are the best measure to use in diagnosis and monitoring.2

Currently, loss of CD26 or CD7 is used for the routine detection of Sézary cells. This study revealed an enormous range across patient samples: 1.13% to 100% and 0.05% to 100% antigen loss, respectively. Importantly, loss of CD26 or CD7 was not restricted to malignant cells; it was also found in reactive (ie, nonmalignant) CD4+ T cells, thus limiting the specificity of conventional flow cytometry for assessing blood tumor burden. EuroFlow gating, aimed at a more comprehensive phenotyping, detected Sézary cells in all samples analyzed in the Najidh et al study. However, aberrant cell marker expression went beyond loss of CD26 and/or CD7 in 92% of the patients. Despite the advantage that this more precise methodology offers, identification of Sézary cells may remain an obstacle due to the complexity of multiparameter flow cytometry, because this tool is not widely available in routine clinical settings. This challenge could be overcome in the future with novel markers such as KIR3DL2, which has proven high diagnostic sensitivity and specificity.3 Notably, initial reports of the clinical use of an anti-KIR3DL2 antibody are promising.4

Although the wide variety of immunophenotypic aberrancies were not linked to previous treatment in this study, heterogeneous phenotypic shifts occurred in patients over time. The authors confirmed that Sézary cells also showed a wide range of T-helper cell phenotypes, encompassing almost all maturation stages investigated, with central memory cells being the most frequent, supporting the current dogma that Sézary cells derive from central memory T cells.5 Interestingly, recent data suggest a skin-resident T-cell origin for Sézary syndrome similar to that in mycosis fungoides, with an ultraviolet (UV) signature of potential driver gene mutations in both entities.6 Of note, data from T-cell biology suggest that CD4+ T-cell clones can exist simultaneously as skin resident and circulating memory cells, even under physiological conditions,7 further supporting the remarkable plasticity of lymphoma cells.8 Najidh et al confirmed the presence of the skin-homing receptor CCR4 at high frequencies in Sézary cells, which is supported by the efficacy data for mogamulizumab, an approved anti-CCR4 therapeutic antibody.

In daily practice, opportunistic infections caused by profound overall immune dysfunction in patients with primary cutaneous lymphoma can be a challenge. Although infections contribute to overall mortality per se in Sézary syndrome, microbial dysbiosis may directly drive disease progression, as shown by immunostimulatory toxins derived from colonization by Staphylococcus aureus.9 Najidh et al postulated that there is an overall imbalanced immune cell homeostasis in patients with Sézary syndrome. They showed that there are altered levels of innate and adaptive circulating leukocytes with a significant reduction of absolute cell counts of CD8+ cytotoxic T cells, B cells, natural killer cells, and others when compared with healthy controls. By contrast, neutrophils, dendritic cells, and monocytes were significantly increased. Transcriptional profiles of monocytes from patients with Sézary syndrome have previously been shown to differ remarkably from those in healthy controls. In vitro, monocytic cytokine expression was reshapened after interferon-γ (IFN-γ) stimulation, which might explain the clinical efficacy of IFN-γ in cutaneous lymphomas.9

Interestingly, differentiation of monocytes into dendritic cells is thought to be relevant for the immunomodulatory

References:

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4. Najidh and colleagues add important insights to the current understanding of immunophenotypic and transcriptional profiles in the circulating malignant cells of patients with Sézary syndrome.1

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