79.5. Hodgkin and Non-Hodgkin Lymphomas: Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma

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Emerging Prognostic Factors for Clinical Care

Several factors are emerging that have prognostic value in patients with CLL/SLL.

Complex Karyotypes. Complex karyotypes, defined as karyotypes with three or more structural abnormalities, are associated with an adverse outcome in SLL/CLL[1-4]; this complexity is not captured by conventional FISH assays. The value of this prognostic marker is limited by the difficulty in obtaining metaphases with conventional techniques. Stimulated karyotypes with CpG oligonucleotides dramatically increase the yield of conventional cytogenetics in SLL/CLL.[5] The importance of complex karyotype recently re-emerged, as it was found to be an important predictor of treatment failure in patients treated with ibrutinib and is independent of *TP53* mutation or del(17p).[6] In patients with relapsed/refractory CLL, CpG-stimulated karyotype may be an important factor for treatment selection in the future.

Minimal Residual Disease (MRD). Prospective studies have shown that assessment of MRD by multiparameter flow cytometry predicts durability of response, PFS, and OS following treatment with chemoimmunotherapy such as fludarabine/cyclophosphamide/rituximab and bendamustine/rituximab. However, its clinical applicability is limited by the lack of standardized evaluation and lack of therapies specifically for patients with MRD after chemoimmunotherapy. Furthermore, the prognostic value of MRD has not been evaluated extensively with the emerging novel agents, such as phosphoinositide 3-kinase inhibitors, Bruton's tyrosine kinase inhibitors, and BH3-mimetics.

CLL-IPI. An international collaboration led by the German CLL Study Group developed a new prognostic index that has excellent discrimination of PFS and OS for patients treated with chemoimmunotherapy. The model was validated in a large independent dataset from the Mayo Clinic. In addition to clinical stage, the index includes several factors known to have an important impact on outcome in patients treated with chemoimmunotherapy: *IGHV* status, del(17p)/*TP53* mutation status, and β_2-microglobulin. These factors are weighted based on the hazard ratios from the statistical model. However, this index has not been applied prospectively, and its value in the current era of novel agents has not been evaluated.

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Factor	*Definition*	*Clinical significance*	*Level of evidence*
Complex karyotype[6]	Conventional or CpG-stimulated karyotype with three or more abnormalities	Predicts clinical resistance to ibrutinib	III
MRD	*MRD negative* is defined as inability to detect CLL-like cells with a sensitivity of 1 in 10-4 by multiparameter flow cytometry	Predicts PFS and OS in patients treated with chemoimmunotherapy	I
CLL-IPI	10-point scoring system: *TP53* mutation or del(17p), 4 points; *IGHV* germline status, 2 points, β_2-microglobulin >3.5 mg/dL, 2 points; Binet B/C or Rai I–IV, 1 point; age >65, 1 point Low risk: 0–1 points; 5-y survival 93% Intermediate risk: 2–3 points; 5-y survival 79% High risk: 4–6 points; 5-y survival 64% Very high risk: 7–10 points; 5-y survival 23%	Modified staging system with superior predictive power compared with Rai/Binet staging system for chemoimmunotherapy	III

Risk Assessment Models

Risk assessment models and prognostic tools play an important role in cancer medicine because they provide a mechanism to integrate disparate data elements into a process that leads to decreased prognostic heterogeneity. Such processes are useful for (1) identifying and characterizing important prognostic factors, (2) improving prognostic predictions for individual patients, and (3) designing, conducting, and analyzing clinical trials.[41] The most common type of prognostic tool is a prognostic calculator that provides time-specific outcome (e.g., 5-year OS) probability predictions for individual

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patients based on their demographic, clinical, and tumor characteristics. The prognostic nomogram developed by Yang et al[42] is an example of a risk calculator. Another type of prognostic tool is a prognostic classifier that places patients into ordered prognostic risk classes (either directly or based on cutoffs for individual probability estimates). The remaining tools referenced in this chapter (e.g., IPI, MIPI, FLIPI, and CLL-IPI) are prognostic classifiers. The AJCC Precision Medicine Core (PMC) developed and published criteria for critical evaluation of prognostic calculators,[43] which are presented and discussed in Chapter 4. The prognostic nomogram developed by Yang et al[42] meets all but one of the AJCC PMC criteria because it lacks discussion of how missing data were treated.

Recommendations for Clinical Trial Stratification

The authors have not provided any recommendations for clinical trial stratification at this time.

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