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The Kaufman/Rubin/Rai Article Reviewed

## **New Menus for CLL Treatment**

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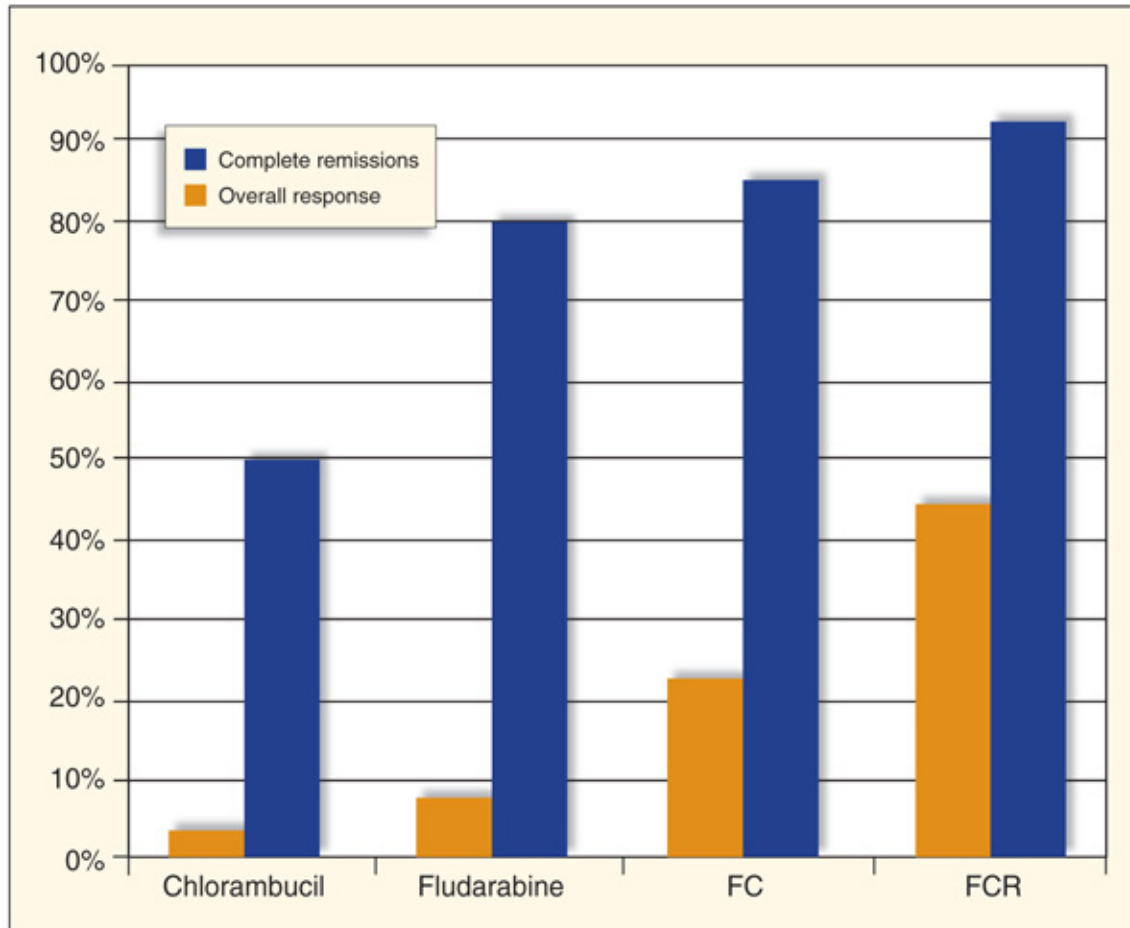
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Chronic lymphocytic leukemia (CLL) is a heterogeneous disease with an extremely variable course. Survival after diagnosis can range from months to decades. As the pathogenesis of the disease is increasingly understood, we begin to unfold the molecular patterns that define the different prognostic subgroups and to develop strategies to predict the clinical course. In addition, a number of more potent treatment modalities have been designed during the past 10 years that allow us to achieve complete remissions in almost 50% of patients and to obtain a treatment-free time of more than 5 years (Figure 1).



**Figure 1: Progress in CLL Therapy During the Past Decade by Combining Different Agents**—Approximate rates of complete remissions and overall responses in first-line treatment as reported by recent randomized trials of various regimens. F = fludarabine, C = cyclophosphamide, R = rituximab.

Fludarabine, bendamustine (Treanda), and two monoclonal antibodies, alemtuzumab (Campath) and rituximab (Rituxan), have been approved by the European and/or American regulatory agencies as novel therapies for CLL. Several novel monoclonal antibodies targeting CD20, CD23, or CD40, as well as drugs designed to interfere with proteins regulating the cell cycle, apoptotic machinery, or leukemic microenvironment (eg, flavopiridol, oblimersen [Genasense], ABT-263, or lenalidomide [Revlimid]) are currently being tested in clinical trials.

Furthermore, the increased experience with reduced-intensity allogeneic

progenitor cell transplantation allows offering this option to physically fit patients. In addition, new prognostic markers that may influence therapeutic decisions have been identified. Novel chemoimmunotherapies have the potential to eradicate CLL beyond the detection level (minimal residual disease, or MRD). The review by Matthew Kaufman, Jason Rubin, and Kanti Rai gives a comprehensive update on these recent developments.

Table 1  
**Algorithm for First- and Second-Line Therapy of Chronic Lymphocytic Leukemia**

Stage	Fitness	Molecular Cytogenetics	First-Line Treatment	
			Standard	Alternatives
Asymptomatic Binet A-B or Rai 0-II	Irrelevant	Irrelevant	None	Only in trials: Treat high-risk patients
	Go-go	No del(17p)	FCR	BR, FR, FA
Binet C or Rai III-IV, or symptomatic disease (any stage)	Go-go	Del(17p)	FCR, A or FA → Allo SCT	
	Slow-go	No del(17p)	Cib	Cib+R, Cib+GA101, B, dose-reduced F or FC or FCR
		Del(17p)	A?	
Relapse	Fitness	Molecular Cytogenetics	Relapse Therapy	
			Standard	Alternatives
Early (< 1 yr) = refractory disease	Go-go	No del(17p)	A or FA → Allo SCT	BR, flavopiridol, lenalidomide
		Del(17p)	A or FA → Allo SCT	Flavopiridol, lenalidomide
	Slow-go	No del(17p)	A	BR, B, lenalidomide
		Del(17p)	A	Lenalidomide
Late (> 1 yr)	Go-go + Slow-go		Repeat first-line treatment	

A = alemtuzumab; Allo SCT = allogeneic stem cell transplantation; B = bendamustine; C = cyclophosphamide; Cib = chlorambucil; F = fludarabine, GA101 = novel anti-CD20 antibody; R = rituximab.

**Practical Algorithm:** The major issue for the practicing hematologist/oncologist is the translation of these developments into a practical, therapeutic concept. This is highly relevant, because CLL is the classical leukemia of the elderly that often requires tailoring the treatment according to the patients’ fitness and ability to tolerate more toxic combination therapies. Today, the choice of CLL therapy becomes increasingly personalized: Thus, the selection of appropriate therapies requires a high degree of professional experience. Therefore, I wish to propose my personal algorithm (Table 1) for the selection of the best treatment option based on three potentially relevant points to consider:

(1) The physical condition (fitness and comorbidity) of the patient, which is

independent of calendar age. (2) The prognostic risk of the leukemia as determined by genetic and other prognostic factors. (3) The Rai or Binet stage of the disease.

Patients with early-stage disease (Binet A/B, Rai 0–II) without symptoms usually do not require therapy. Early treatment is currently tested in clinical trials for patients at high risk. In patients with advanced (Binet C, Rai III–IV) or active, symptomatic disease, treatment should be initiated. In this situation, patients need to be evaluated for their physical condition (or comorbidity). To patients in good physical condition (“go-go”), as defined by a normal creatinine clearance and a low score on the cumulative illness rating scale (CIRS), [1] an FCR combination therapy should be offered. Patients with relevant comorbidity (“slow-go”) may be offered either chlorambucil (Leukeran) or a dose-reduced fludarabine-containing regimen for symptom control.

Patients with symptomatic disease and with del(17p) or p53 mutations respond poorly to fludarabine or FC, and show a response rate of approximately 50% to alemtuzumab monotherapy or combination therapy, as well as to FCR, but these responses usually have a short duration of a few months to 1.5 years. [2–4] Therefore, these patients should be treated within experimental protocols, and it should be proposed that they undergo an allogeneic stem cell transplant whenever possible. Patients with del(17p) may respond to alemtuzumab monotherapy or combination therapy. [5]

**Second-Line Treatment:** For second-line treatment, the first-line treatment may be repeated if the duration of the first remission exceeds 12 months (or, with modern chemoimmunotherapies, 24 months). The choice becomes more difficult and limited in treatment-refractory CLL (as defined by an early relapse within 6 months after the last treatment) or in cases with the chromosomal aberration del(17p). In principle, the initial regimen should be changed. The following options exist:

- Alemtuzumab alone or in combination [6,7]

- Flavopiridol (in clinical trials)[8]
- Lenalidomide (if available or in clinical trials)[9]
- Allogeneic stem cell transplantation with curative intent.[10]

The choice of one of these options depends on the fitness of the patient. According to recent consensus group recommendations from the European Group for Blood & Marrow Transplantation (EBMT), physically fit patients with refractory CLL or with del(17p) should be offered an allogeneic transplantation, since their prognosis has remained extremely poor with conventional therapies.[10]

Finally, and in full agreement with the authors of this review, it is important to emphasize that CLL patients should be treated within clinical trials whenever possible. The choice of treatment options demands the continued optimization of our current therapeutic algorithm for this incurable disease.