Ibrutinib has robustly increased progression-free survival (PFS) in CLL [Byrd JC et al. *N Engl J Med.* 2013], although patients with deletions in the short arm of chromosome 17 remain a high-risk group. In CLL, del(17p) is often associated with CKT involving multiple unrelated abnormalities [Haferlach T et al. *Leukemia.* 2007]. Genes conferring treatment resistance exist in patients with del(17p) and/or CKT [Woyach JA et al. *N Engl J Med.* 2014]. The significance of CKT in the outcome of ibrutinib treatment of CLL is unclear.

This study analyzed 100 CLL patients (median age 65 years) treated a median of twice with ibrutinib-based regimens from mid-2010 to mid-2013. The majority of patients (60%) were Rai stage III-IV and lacked immunoglobulin heavy chain variable mutations (81%). A minority (19%) were refractory to fludarabine therapy. Use of fluorescence in-situ hybridization (FISH) revealed prevalence of del(17p), del(11q), CKT, and other mutations in 48%, 28%, 42%, and 24% of patients, respectively. Of the 32 patients with del(17p) and 33 with no del(17p) for whom metaphase karyotype data were available, 23 and 4, respectively, harbored CKT.

The median follow-up was 27 months (range, 11 to 48 months). Eight patients who underwent planned allogeneic stem cell transplant were censored for event-free survival (EFS) analysis. In 36 patients treated with ibrutinib + rituximab, complete response rate (CRR) was 8%. In 14 patients treated with ibrutinib + bendamustine + rituximab, CRR was 50% ($P = .001$), and the significance remained in multivariable analysis. Overall rates and CRRs did not differ significantly between patients with or without del(17p), del(11q), and other mutations, or those with or without CKT. The presence of del(17p) was associated with significantly worse EFS.

EFS was also significantly worse for patients with CKT vs no complex karyotype (12/27 vs 31/38; $P < .0001$) and in patients with del(17p) and CKT vs those with del(17p) alone (11/23 vs 7/9; $P = .047$). In the absence of CKT, patients with del(17p) or del(11q) had similar EFS (7/9 vs 9/10; $P = .516$). Multivariable analysis revealed the significant association of CKT with EFS (HR, 5.3; 95% CI, 1.5 to 19.2; $P = .011$).

The most frequent event was progression of CLL (n = 10), followed by death (n = 8), and Richter transformation (n = 5). In 27 patients with CKT and 38 patients without CKT, CLL progression was evident in 5 and 1 patients, respectively. Overall survival in all patients was not significantly different.

Patients refractory to fludarabine had significantly worse overall survival (10 of 19 died) than those not refractory to fludarabine (19 of 81 died) ($P = .009$). Multivariable analysis revealed significant association of fludarabine-refractory disease with worse overall survival (HR, 6.4; 95% CI, 1.8 to 22.8; $P = .004$).

The data implicate CKT as a more important predictor of outcome than del(17p). Absence of CKT is associated with less frequent disease progression. When progression occurs, it tends to occur > 12 months after ibrutinib treatment, with death soon after.

The researchers concluded that patients with CKT are an ideal group in which to study novel treatments.

MRD and Clinical Response Predictors of PFS in CLL

Written by Brian Hoyle

Barbara Eichhorst, MD, Center of Integrated Oncology Cologne-Bonn, University Hospital Cologne, Cologne, Germany, presented on behalf of the German CLL Study Group on the value of minimal residual disease (MRD) in combination with clinical response as a predictor of progression-free survival (PFS) in chronic lymphocytic leukemia (CLL).

The study was based on previous observations that correlated PFS and overall survival (OS) with MRD level in patients with partial response (PR) and complete response (CR), with increasingly worse outcomes in PFS and OS [Strati P et al. *Blood.* 2014; Boettcher S et al. *J Clin Oncol.* 2012]. To evaluate the relevance of MRD testing from peripheral blood with clinical response, 1378 patients treated with fludarabine/cyclophosphamide vs fludarabine/cyclophosphamide/rituximab (FCR) in 1 German CLL Study Group trial and with FCR vs bendamustine/rituximab in another trial were analyzed to identify the target population, composed of 555 patients who achieved CR or PR for whom MRD measurements from peripheral blood were available at the end of the trial. The target and nontarget populations were comparable at baseline (Table 1).

MRD negativity was associated with significantly improved CR (median PFS, 68.9 vs 44.4 months; $P = .004$) and PR (median, 61.7 vs 28.1 months; $P < .001$). The improved MRD negativity–associated PR was significantly longer than the CR ($P = .047$). For OS, MRD positivity was associated with significantly worse PR. Multivariate analysis revealed significance between positive vs negative MRD status (HR, 3.487; 95% CI, 2.678 to 4.541; $P < .001$), PR vs CR (HR, 1.420; 95% CI, 1.075 to 1.876; $P = .014$), presence of del(17p) (HR, 9.082; 95% CI, 4.325 to 19.072; $P < .001$), and unmutated vs mutated immunoglobulin heavy chain variable (HR, 2.582; 95% CI, 1.930 to 3.455; $P < .001$).

The second portion of the study evaluated the MRD-negative target population for the clinical relevance of

Table 1. Baseline Characteristics and Prognostic Factors

Characteristics and Factors	Population	
	Nontarget (n = 823)	Target (n = 555)
Treatment		
FC	35.0	21.8
FCR	48.1	53.0
BR	16.9	25.2
Age, y[a]	61 (30-81)	61 (33-81)
Male	71.3	77.1
ECOG[a]	0 (0-2)	0 (0-2)
CIRS[a]	1 (0-8)	2 (0-7)
Binet stage		
A	10.8	13.7
B	54.8	51.3
C	34.3	35.0
Genetic aberrations by FISH		
del (17p)	6.9	1.5
del (11q)	21.7	25.0
IGHV unmutated	62.5	62.1
s-TK (U/L) > 10.0	74.0	74.1
s-β2m (mg/L) > 3.5	33.4	33.9

Values in percentage unless noted otherwise.

BR, bendamustine/rituximab; CIRS, Cumulative Illness Rating Scale; ECOG, Eastern Cooperative Oncology Group; FC, fludarabine/cyclophosphamide; FCR, fludarabine/cyclophosphamide/rituximab; FISH, fluorescence in situ hybridization; IGHV, immunoglobulin heavy chain variable; TK, tyrosine kinase.

[a]Median (range).

Table 2. PFS Grouped by MRD−PR Subgroups

	Median PFS, mo	*P* Value[a]
MRD−		
CRs	68.9	—
PRs		
With splenomegaly	72.0	.331
With lymphadenopathy	38.7	< .001
With bone marrow	56.8	.420
> 1 above	51.8	.202
MRD+		
CRs	44.4	.004
PRs	28.1	< .001

BM, bone marrow; CR, complete response; MRD, minimal residual disease negative (-) or positive (+); PFS, progression-free survival; PR, partial response.

[a]Compared with MRD⁻ CRs.

splenomegaly, lymph node enlargement, and bone marrow involvement at response assessment in MRD-negative patients. The analysis centered on patients with only lymphadenopathy (n = 25), only bone marrow involvement (n = 18), only splenomegaly (n = 78), and > 1 involvement (n = 40). The respective median PFSs were 38.7, 56.8, 72.0, and 51.8 months. The median PFS was significantly lower in patients with lymph node enlargement ($P < .001$; Table 2). No improvement in OS was evident.

Finally, PFS in MRD-negative patients displaying a PR was assessed using different cutoffs for normal spleen size on radiologic examination in the patients with only lymphadenopathy. PFS was not appreciably affected by use of a splenomegaly cutoff exceeding 12 cm in patients with only bone marrow involvement, only splenomegaly, lymph node enlargement, and > 1 involvement.

The data indicate that MRD and clinical response are strong predictors of PFS, with the 2 together providing a more accurate prediction of PFS than clinical response alone. Finally, splenomegaly as the only anomaly at the end of the trial had no influence on PFS in the MRD-negative patients who displayed PR.

Noninvasive Detection of Genomic Imbalances in HL Is Promising

Written by Lynne Lederman

Although Hodgkin lymphoma (HL) is highly curable today, this comes at the expense of treatment-related toxicities, underscoring the need to identify patients who would be candidates for less intensive therapy regimens. There is also a fraction of 10 to 15% of patients who will not be cured by first-line therapy, who will be difficult to manage, and who are equally difficult to identify upfront. The development of effective therapies has taken place despite limited knowledge of only the biology of this disease: this is related to the low abundance of the Hodgkin/Reed-Sternberg (HRS) cell, the malignant cell in HL, which is present as only 0.1% to 2% of the total cells in HL biopsies and is outnumbered by inflammatory cells in the microenvironment. The rarity of these cells has been an obstacle to sequencing or genomic studies of HL. Purification of HRS cells by