The clinical benefit of vosaroxin combination therapy may be underestimated in younger patients due to the high rate of SCT. All-cause mortality was similar for both groups at 30 and 60 days. The most common serious adverse events were febrile neutropenia, sepsis, pneumonia, bacteremia, and stomatitis, and were higher in the vosaroxin group but these did not translate to excess mortality. Serious and nonserious cardiac, renal, neurologic, and hepatic adverse events were comparable between treatment groups. Vosaroxin plus cytarabine provides patients with relapsed, refractory AML with a new option for salvage therapy.

FCR Superior in Treatment of Advanced CLL

Written by Brian Hoyle

Barbara Eichhorst, MD, Center of Integrated Oncology Cologne-Bonn, University Hospital Cologne, Cologne, Germany, described the confirmation of the superiority of a frontline chemotherapy with a regimen involving fludarabine plus cyclophosphamide plus rituximab (FCR) compared with bendamustine plus rituximab (BR) in previously untreated, physically fit patients with advanced chronic lymphocyte leukemia (CLL).

The study was prompted by results from the researchers' previous demonstration of significantly better overall survival in CLL patients treated with FCR compared with BR. Presently, 564 physically fit patients with untreated and active CLL, and no deletions in chromosome 17p were randomized to receive FCR intravenously (n = 284; fludarabine 25 mg/m^2, days 1–3; cyclophosphamide 250 mg/m^2, days 1–3; and rituximab 375 mg/m^2, day 0 in cycle 1 and 500 mg/m^2, day 1 during cycles 2-6) or BR intravenously (n = 280; bendamustine 90 mg/m^2, days 1–2; rituximab 375 mg/m^2, day 0 in cycle 1 and 500 mg/m^2, day 1 during cycles 2-6).

The study arms were comparable at baseline with the exceptions of a greater proportion of patients aged > 65 years (30.5% vs 38.7%; $P = .042$), greater mean number of cycles (5.27 vs 5.41; $P = .022$), and prevalence of immunoglobulin heavy chain variable (IGHV) mutations (55.3% vs 67.8%; $P = .003$) for the BR arm.

The intention-to-treat population received FCR (n = 282) and BR (n = 279). The primary end point of progression-free survival (PFS) in the intention-to-treat population during the follow-up observation time was reached, with a hazard ration of 1.6 that was statistically significant.

During a median observation time of 37.1 months (range, 0-59.9 months), complete response was observed in 39.7% and 30.8% of patients in the FCR and BR arms, respectively ($P = .034$). The overall response rate was comparable in the FCR and BR arms (95.4% and 95.7%, respectively; $P = 1.0$). Those treated with FCR achieved higher rates of minimal residual disease at all time points (Table 1).

Table 1. Minimal Disease Negativity

MRD Negativity	FCR, % (n/N) (n = 282)	BR, % (n/N) (n = 279)
BM at FR	26.6 (75/282)	11.1 (31/279)
PB at FR	48.6 (137/282)	38.4 (107/279)
PB 12 mo after FR	19.7 (47/238)	9.0 (20/222)
PB 18 mo after FR	18.0 (37/206)	8.5 (16/187)

BM, bone marrow; BR, bendamustine/rituximab; FCR, fludarabine/cyclophosphamide/rituximab; FR, final restaging; MRD, minimal disease negativity; PB, peripheral blood.

The FCR regimen produced significantly better PFS in patients treated with unmutated IGHV than the BR regimen (42.7 vs 33.6 months; $P = .017$), but not in patients with mutated IGHV (not reached vs 52.0 months; $P = .153$). The FCR regimen was significantly more beneficial than the BR regimen in terms of PFS in patients aged ≤ 65 years (53.6 vs 38.5 months; $P < .001$) but not in older patients (not reached vs 48.5 months; $P = .170$). Overall survival was similar (FCR, 90.6%; BR, 92.2%; $P = .897$).

Neutropenia was more frequent in the FCR arm (84.2% vs 59.0%; $P < .001$), as was thrombocytopenia (21.5% vs 14.4%; $P = .03$), all infections (39.1% vs 26.8%; $P < .001$), and infections during the first 5 months after therapy (11.8% vs 3.6%; $P < .001$). Those aged > 65 years treated with FCR were significantly more likely to experience infection (47.7% vs 20.6%; $P < .001$).

The data demonstrate the inferiority of BR vs FCR with respect to PFS and complete response rate and the association of FCR with higher rates of neutropenia and severe infection. The researchers concluded that FCR remains as the standard therapy in fit patients, with BR considered as alternative treatment in fit, but elderly, patients.

CKT Implicated in Worse Outcomes With Ibrutinib Therapy of CLL

Written by Brian Hoyle

Philip A. Thompson, MBBS, University of Texas MD Anderson Cancer Center, Houston, Texas, USA, reported that complex metaphase karyotype (CKT), defined as ≥ 3 unrelated abnormalities, rather than del(17p), is linked with inferior outcomes in patients with chronic lymphocytic leukemia (CLL) treated with ibrutinib who relapse or are fludarabine-refractory.

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