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

laser microdissection has been done by some for molecular studies or gene expression profiling. Although it is an elegant approach, it is labor-intensive, time-consuming, and not applicable on a large scale.

Peter Vandenberghe, MD, PhD, Center for Human Genetics, Leuven, Belgium, discussed the noninvasive detection of genomic imbalances in HRS cells in early and advanced-stage HL by sequencing of circulating cell-free DNA (ccfDNA) in plasma. His group applied massive parallel sequencing to ccfDNA in a prospective study of patients with biopsy-proven stage IIA to IVB nodular sclerosis classical HL (NSHL). The pipeline used was developed for noninvasive prenatal testing, allowing genome-wide detection of fetal aneuploidies and segmental imbalances. In one pregnant patient, a complex profile with several genomic imbalances was identified. After exclusion of fetal and maternal constitutional abnormalities, the possibility of a maternal or fetal tumor was considered, leading to a biopsy-proven diagnosis of early-stage (IIA) NSHL in the pregnant mother. To verify the origin of the genomic imbalances, HRS cells in formalin-fixed paraffin-embedded biopsy specimens were investigated by fluorescence in situ hybridization (FISH). HRS cells were identified by the size of their nucleus and CD30 immunostaining; gains of 8q24, 9p24, and 14q were found in these cells, which matched with imbalances in the ccfDNA profile; and this strongly suggested that DNA derived from them was causing the abnormal ccfDNA profile in this patient.

The group then conducted a prospective study in NSHL. In 9 additional patients examined (2 with stage IVB disease, and 7 with stage IIA disease), genomic imbalances were identified in 8 patients by massive parallel sequencing of ccfDNA. The profiles were most pronouncedly abnormal in patients with stage IV disease. The regions that were recurrently imbalanced in this series have all previously been described in the literature based on array comparative genomic hybridization on microdissected HRS cells. These imbalances were also validated by FISH analysis of HRS cells from biopsies from all patients. Although several imbalances were identified as recurrent, they did not occur uniformly: As such, profiling of ccfDNA promises to reveal patient heterogeneity. More patients need to be studied in order to identify patterns of imbalances and their frequency, as well as to tune the technology to the context of noninvasive cancer testing rather than noninvasive prenatal diagnosis.

All patients in this study were treated and reached complete remission. This was paralleled by rapid normalization of the ccfDNA profiles. Therefore, ccfDNA profiling also appears promising for noninvasive disease monitoring.

Dasatinib Outcomes Maintained Over 5 Years

Written by Emma Hitt Nichols, PhD

After 5 years of follow-up, patients with chronic-phase chronic myeloid leukemia (CML) who were treated with dasatinib experienced greater rates of major molecular response (MMR) and molecular response (MR), but similar rates of overall survival (OS) and progression-free survival (PFS) compared with patients treated with imatinib. Jorge Cortes, MD, University of Texas MD Anderson Cancer Center, Houston, Texas, USA, presented the final 5-year data from the Phase 3 Study of Dasatinib vs Imatinib in Patients With Newly Diagnosed Chronic Phase CML [DASISION; NCT00481247].

Dasatinib is a first-line treatment for patients with chronic-phase CML. In the DASISION trial, patients with chronic-phase CML who received dasatinib demonstrated higher rates of complete cytogenic response (CCyR) and a faster rate of attaining MR with an acceptable safety profile compared with patients who received imatinib [Kantarjian H et al. *N Engl J Med.* 2010]. The purpose of the present analysis was to determine the long-term outcomes of patients who completed a minimum of 5 years of follow-up.

The multicenter DASISION trial randomly assigned 519 treatment-naïve patients with chronic-phase CML to receive dasatinib 100 mg QD (n = 259) or imatinib 400 mg QD (n = 260) [Kantarjian H et al. *N Engl J Med.* 2010]. The primary end point of confirmed CCyR by 12 months was reached by 77% of patients in the dasatinib arm compared with 66% of patients in the imatinib arm ($P = .007$).

By 5 years, the MMR rates were 76% and 64% in the dasatinib and imatinib arms, respectively ($P = .0022$); the difference between the 2 arms remained similar over the 5-year period. MR was achieved by 42% and 33% of patients in the dasatinib and imatinib arms, respectively ($P = .0251$). However, the 5-year OS and PFS were similar among both arms, with rates of 91.5% (HR, 1.01; 95% CI, 0.58 to 1.73) and 85.5% (HR, 1.06; 95% CI, 0.68 to 1.66), respectively. A greater number of patients in the imatinib arm (7.3%) experienced transformation to accelerated or blastic phase CML compared with the dasatinib arm (4.6%).

Table 1 outlines the outcomes at 5 years in relation to the MR at 3 months; patients in both treatment groups whose BCR-ABL levels were ≤ 10% at 3 months had better outcomes.

In addition, 5-year OS, PFS, and transformation-free survival were significantly higher in patients whose BCR-ABL levels were ≤ 10% at 3 months in both arms of the