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

Table 1. Best 5-Year Responses by Molecular Response at 3 Months

Response	Dasatinib 100 mg QD (n = 259)		Imatinib 400 mg QD (n = 260)	
BCR-ABL at 3 mo	≤10 (84)	>10 (16)	≤10 (64)	>10 (36)
CCyR	94	41	92	59
MMR	87	38	81	41
MR[4.5]	54	5	48	12

Response is given in percentages.

CCyR, complete cytogenic response; MMR, major molecular response; MR molecular response.

Table 2. Five-Year Outcomes by Molecular Response at 3 Months

Outcome	Dasatinib 100 mg QD (n = 259)		*P* Value	Imatinib 400 mg QD (n = 260)		*P* Value
BCR-ABL at 3 mo	≤10 (84)	>10 (16)		≤10 (64)	>10 (36)	
Estimated 5-y OS	94	81	.0028	95	81	.0003
Estimated 5-y PFS	89	72	.0014	93	72	<.0001
Estimated 5-y TFS	97	83	.0004	97	80	<.0001

Data are for on-study treatment and in follow-up after discontinuation of randomized treatment. Response is given in percentages.

OS, overall survival; PFS, progression-free survival; TFS, transformation-free survival.

study compared with patients whose BCR-ABL levels were >10% (Table 2).

Treatment failure occurred in 10 patients in the dasatinib arm and 14 patients in the imatinib arm, and disease progressed in 18 patients in the dasatinib arm and 23 patients in the imatinib arm. Mutations were identified in some patients whose treatment failed or disease progressed, and most of these patients discontinued the study early.

Important adverse events included pleural effusion, which occurred in 28% of patients who received dasatinib and only 1% of patients who received imatinib. In addition, arterial ischemic events such as myocardial infarction, angina pectoris, coronary artery disease, acute coronary syndromes, and transient ischemic attack occurred more frequently in the dasatinib arm. Other adverse events reported more frequently in the dasatinib arm included abdominal pain and headache, whereas facial edema, muscle spasms, myalgia, nausea, and vomiting occurred more frequently in the imatinib arm.

In conclusion, Dr Cortes stated that the 5-year data from the DASISION trial support the data from earlier analyses showing that dasatinib treatment resulted in higher rates of MMR and MR, faster time to MR, and less frequent transformation to accelerated or blastic CML. No new safety signals occurred. Although arterial ischemic events were more frequent with dasatinib treatment, they were uncommon.

Reduced-Dose Conditioning Comparable to Standard Dose Prior to ASCT in MDS

Written by Emma Hitt Nichols, PhD

Reduced-dose conditioning prior to allogenic stem cell transplantation (ASCT) in patients with myelodysplastic syndrome (MDS) or secondary acute myeloid leukemia (sAML) resulted in similar outcomes including nonrelapse mortality, incidence of relapse, and relapse-free survival compared with standard-dose conditioning. Nicolaus Kröger, MD, University Cancer Center Hamburg, Hamburg, Germany, presented data from the Dose-Reduced Versus Standard Conditioning in MDS/sAML trial [RICMAC; NCT01203228].

Currently, the most effective, potentially curative, treatment for MDS is ASCT. In favor of reducing toxicity, dose-reduced conditioning is being increasingly used; however, some retrospective data suggest that dose-reduced conditioning may lead to higher rates of relapse. The purpose of the RICMAC trial was to evaluate the effect of reduced-dose conditioning on the outcomes of patients with MDS or sAML after ASCT.

In the prospective, open-label, phase 3 RICMAC trial, patients (n = 129) with MDS or sAML were randomly assigned to receive standard-dose busulfan (12.8 mg/kg ideal body weight [IBW] intravenously [IV] or 16 mg/kg body weight [BW] orally) plus cyclophosphamide (120 mg/kg BW IV) or reduced-dose busulfan (6.4 mg/kg IBW IV or 8 mg/kg BW orally) plus fludarabine (5×30 mg/m^2 IV). Patients were considered to have cytologically proven MDS based on refractory anemia or refractory anemia with ring sideroblasts, excess blasts, or excess of blast in transformation. Patients with chronic myelomonocytic leukemia and sAML were also included. All patients had a blast count <20% regardless of chemotherapy at the time of ASCT. Other eligibility criteria included human leukocyte antigen (HLA)–matched related donors aged 18 to 65 years or unrelated donors aged 18 to 60 years