Prospective Use of Ultra-Low Coverage Whole Genome Sequencing of ccfDNA in a Routine Setting for Multiple Myeloma

Rengifo, Laura Yissel, Department of Human Genetics, KU Leuven, Leuven, Belgium
Smits, Sanne, Department of Human Genetics, KU Leuven, Leuven, Belgium
Buedts, Lieselot, Department of Human Genetics, KU Leuven, Leuven, Belgium
Delforge, Michel, Department of Hematology, University Hospitals Leuven, Leuven, Belgium
Dehaspe, Luc, Center for Human Genetics, University Hospitals Leuven, Leuven, Belgium
Tousseyn, Thomas, Laboratory for Translational Cell and Tissue Research, Department of Imaging and Pathology, KU Leuven, Leuven, Belgium
Boeckx, Nancy, Laboratory Medicine, University Hospitals Leuven, Leuven, Belgium / Department of Oncology, KU Leuven, Leuven, Belgium
Lehnert, Stefan, Genomics Core, KU Leuven, Leuven, Belgium
Michaux, Lucienne, Center for Human Genetics, University Hospitals Leuven, Leuven, Belgium
Vermeesch, Joris Robert, Center for Human Genetics, University Hospitals Leuven, Leuven, Belgium
Vandenberghe, Peter, Department of Human Genetics, KU Leuven / Department of Hematology, University Hospitals Leuven, Leuven, Belgium
Dewaele, Barbara, Center for Human Genetics, University Hospitals Leuven, Leuven, Belgium

ABSTRACT

Chromosomal abnormalities in multiple myeloma (MM) found in bone marrow plasma cell samples (BM-PCs) are important for prognostic risk stratification, but variable infiltration of these cells or failed aspiration can impede the analysis. Cytogenetic profiling with FISH BM-PCs is the current gold standard technique used but ultra-low coverage sequencing (ULCS) of circulating cell-free DNA (ccfDNA) may offer a minimally invasive alternative. In this study we compared ULCS, aCGH and FISH from BM-PCs performed in a routine setting with ULCS of ccfDNA for the detection of somatic copy number aberrations (CNAs) in MM.

Methods: Purified CD138+ BM-PCs were obtained from 23 MM patients, including 14 newly diagnosed cases, five at the time of progression and 4 at relapse, prior to treatment initiation. These cells were analyzed with aCGH, FISH and ULCS following the routine protocols from the diagnostics laboratory. Paired samples of peripheral blood-ccfDNA were evaluated by ULCS using the IchorCNA pipeline and the results were compared to those found in BM-PCs.

Results: Cytogenetic markers were identified in 18 patients; five cases were excluded due to low tumor fraction (TF; ≤3%). ULCS, aCGH and FISH were used on BM-PCs of 10 patients, while for eight only FISH was used due to the low amount of PCs in the BM. In 83% of the ccfDNA CNA profiles we found high concordance with the results of routine FISH and/or BM-PCs ULCS and aCGH in BM-PCs. This comparison resulted in the same risk classification although CNA analysis does not provided information about translocations. On average, 16 CNAs per patient were found in ccfDNA. Compared to BM-PCs, three additional CNAs were found in ccfDNA that were not detected in BM-PCs, but none of these additional CNAs was clinically significant. Chromothripsis was detected in five patients and these patients had the highest values of TF (range 7.1% to 42%) in our series. This suggests a potential use of TF values as an informative biomarker of risk.

Conclusion: ULCS of ccfDNA is effective due to its simplicity and repeatability. We validated the detection of copy number abnormalities in ccfDNA. This proof-of-principle study suggests that ULCS of ccfDNA can contribute to determining risk stratification in MM, especially in cases where BM-PC purification fails.