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ORAL ABSTRACTS

651.MULTIPLE MYELOMA AND PLASMA CELL DYSCRASIAS: BASIC AND TRANSLATIONAL

Kinetics and Biology of Circulating Tumor Cells (CTCs) and Measurable Residual Disease (MRD): Two Dynamic High-Risk Clones in Multiple Myeloma (MM)

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BACKGROUND

CTCs and MRD are two small clones associated with a high risk of progression in smoldering MM (SMM) and post treatment relapse in active MM. Despite growing knowledge about their clinical significance and biological features, these questions remain unanswered: 1) What is the prognostic value of CTC and MRD kinetics? 2) Is MM dissemination and on-treatment resistance driven by specific genomic alterations? 3) Are CTCs and MRD genetically related?

AIM

Analyze the kinetics and molecular features of CTCs and MRD in SMM and MM patients.

METHODS

CTC kinetics were investigated using NGF in 164 SMM patients with ≥3 assessments collected every 6 months in the iMMunocell study. MRD kinetics were investigated using NGF in 277 MM patients with ≥4 assessments in BM aspirates after induction, transplant, consolidation, and yearly during maintenance (GEM2012MENOS65-GEM2014MAIN trials). Unsupervised clustering based on CTC and MRD kinetics was performed using CONNECTOR.

Molecular features of BM tumor cells at diagnosis were compared to paired CTCs in 94 SMM and MM patients and to paired MRD in 96 MM patients. In 10 cases, genomic data from tripartite BM tumor cells, CTCs, and MRD was available. Tumor samples were isolated based on patient-specific aberrant phenotypes using FACS. Whole exome and RNA-seq were performed in 343 and 217 samples, respectively.

RESULTS

Based on the assessment of CTCs in 754 PB samples, SMM patients clustered into 3 groups: sustained undetectable (n = 20), stable (n = 71) and evolving (n = 73) CTC levels. With a median follow-up of 2 years, the respective 2y progression-free rates were 100%, 94% and 81% (P =.003). Risk stratification based on CTC kinetics (C-index 0.68) outperformed a single baseline assessment (C-index 0.61) and, along with the IMWG 20/2/20 model, had independent prognostic value (HR 3.4; P = .01). Patients with high risk cytogenetics showed more frequently evolving CTC levels. Studying genetic drivers of tumor egress, we found CTCs to closely resemble BM tumor cells (88% concordance at copy number [CNA] and somatic mutational [SNV] level). No recurrent cell-specific SNV or CNA was identified. CTC's transcriptional profile revealed 268 DEGs enriched in interferon alpha, gamma response and cell-adhesion pathways.

Next, the prognostic value of MRD dynamics was analyzed according to 1,759 assessments, identifying 3 patient clusters: sustained undetectable (n = 100), stable (n = 104), and evolving (n = 73) MRD levels. Respective 6-year rates of PFS after consolidation were 90%, 75% and 5% (P <.001), and of OS were 94%, 95% and 66% (P<.001). Risk stratification based on MRD kinetics (C-index 0.82) outperformed a single MRD assessment before maintenance (C-index 0.62), the R-ISS (C-index 0.57) and R2-ISS (C-index 0.61) at diagnosis. MRD cells showed heterogeneous genomic evolution (60% median concordance) diverging from BM tumor cells at diagnosis due to *de novo* CNA and SNV that emerged at a subclonal level, particularly after transplant. After induction, MM driver mutations were detected or remained clonal in 13/19 (68%) MRD, whereas after transplant, this was true for only 5/13 (38%) MRD. No recurrent cell-specific SNV or CNA was identified. The transcriptional signature of MRD was treatment dependent, with common molecular features of on-treatment resistance found in all 96 patient-paired samples analyzed after various treatment stages. The 334 DEGs were commonly enriched in *KRAS* signaling hallmarks.

Genomic profiles of tripartite BM tumor cells, CTCs and MRD from 10 MM patients confirmed a patient-specific mutational landscape with genomic heterogeneity in MRD. For instance, one patient exhibited *BRAF* & *DIS3* mutations and del(13q) detected at baseline in BM tumor cells and CTCs, which persisted in MRD. After induction, *de novo* clonal SNVs, including a *NEK11* mutation, emerged, followed by the appearance of 3 subclonal CNA after transplant, possibly contributing to resistance.

CONCLUSIONS

This is the largest dataset analyzing the kinetics and molecular features of CTCs and MRD in SMM and active MM. We showed superior prognostic value of CTC and MRD kinetics over single assessments. Tumor dissemination seems to be driven by transcriptional priming rather than acquired secondary genetic events, while on-treatment resistance is linked to genomic and transcriptional evolution, without recurrent genetic alterations and with common molecular signatures of resistance.

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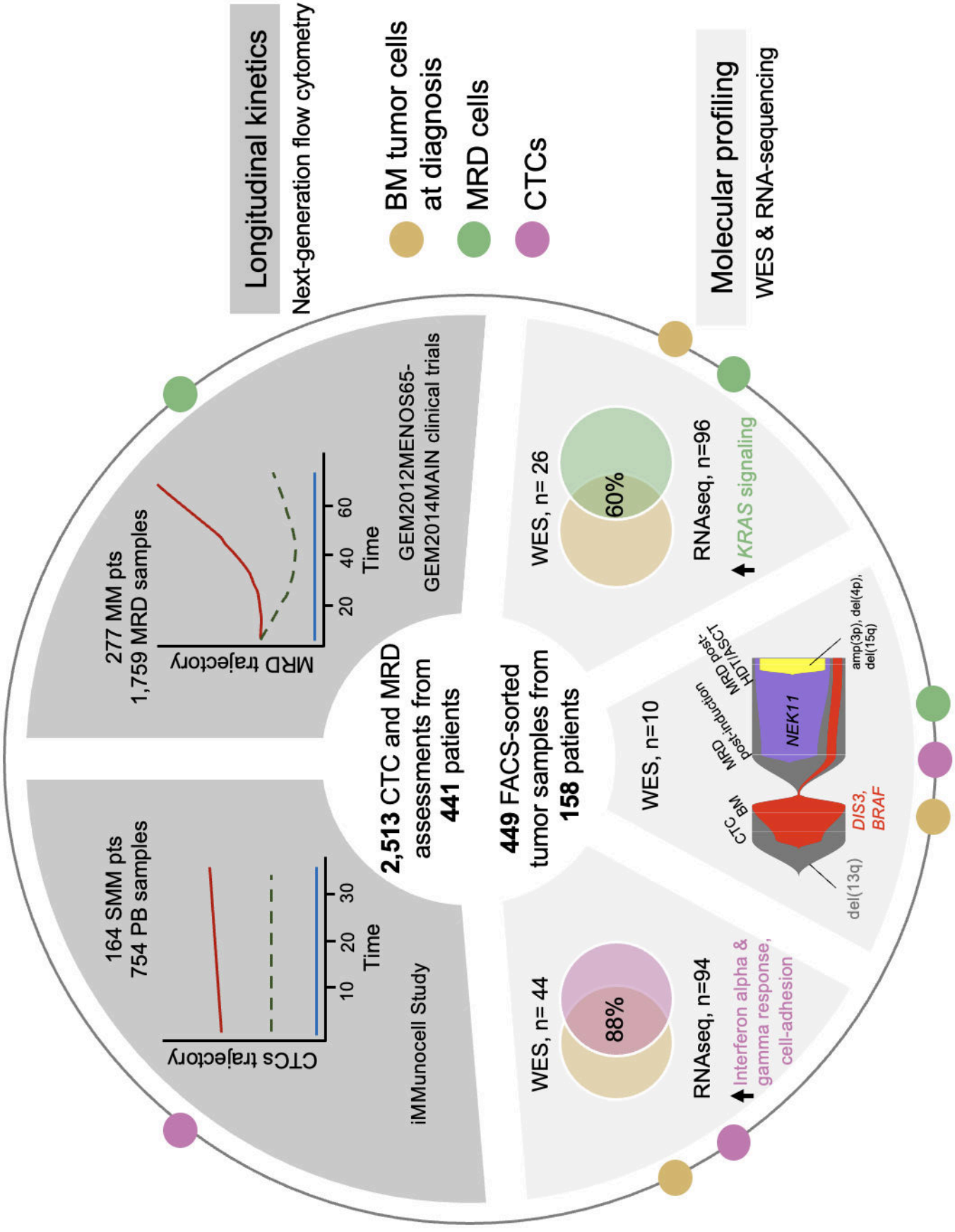

Figure 1