2. NEWLY DIAGNOSED MULTIPLE MYELOMA

BLOOD-BASED RISK STRATIFICATION OF MYELOMA PATIENTS USING CIRCULATING TUMOR CELLS: RESULTS FROM THE EUROPEAN CTC CONSORTIUM

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Background. Circulating tumor cells (CTCs) are emerging biomarkers in multiple myeloma (MM) and may aid patient stratification when cytogenetic data is incomplete or unavailable. The observation that CTCs exist along a continuum challenges the concept of primary plasma cell leukemia (pPCL) as a distinct entity, suggesting that the conventional CTC threshold reflects a point on a broader biological spectrum rather than a fundamentally different disease.

Methods. We analyzed data from 2,406 patients with newly diagnosed MM and CTC tested by flow cytometry and 118 with pPCL (CTC >5%) included in the European CTC Consortium (Czech Republic, Greece, Italy, HOVON/Netherlands-Belgium, France, PETHEMA/Spain). Cytogenetic risk [del(17p), t(4;14), t(14;16)] was assessed by FISH; median follow-up was 5 years. A blood-based risk model named CTC-staging system (CTC-SS) was developed using CTC levels, ISS stage, and LDH, with increasing scores for higher CTC percentages. The presence of the risk factor gives a score that is proportional to the beta of the risk feature in the Cox regression for progression-free survival (PFS; e.g. CTC 0.002-0.02% , 1 point; CTC 0.02-0.2%, 2 points). PFS outcomes were compared across MM patients with varying CTC levels and pPCL subgroups (CTC 5–20% and >20%).

Results. CTC distribution among NDMM patients was: <0.002% (26%), ≥0.002–<0.02% (24%), ≥0.02–<0.2% (28%), ≥0.2–<2% (14%), 2–5% (3%), and >5% (5%). FISH data were incomplete in 30% of cases. The CTC-SS classified patients in 3 risk groups, I (31%), II (53%), and III (16%). Median PFS were 83 months for CTC-SS I, 38 months for CTC-SS II and 21 months for CTC-SS III (Figure 1a). The model performed similarly to R-ISS (PFS C-index 0.599 vs. 0.584) and is applicable when cytogenetics is missing. Outcomes of patients with extremely high CTC levels did not differ significantly from those considered currently as pPCL (>5%), with overlapping PFS among patients with CTC 2–5%, 5–20%, and >20% (Figure 1b). Higher CTC levels correlated with enrichment of specific genetic lesions, notably t(14;16), t(14;20), t(11;14), del(17p), and amp(1q) (Figure 1c).

Conclusions. The CTC-SS provides a practical, blood-based staging tool for newly diagnosed MM when cytogenetic data are unavailable, performing comparably to R-ISS without the need of a bone marrow evaluation. Patients with CTC levels ≥2% show similar PFS outcomes with those >5% or >20%, suggesting that a log-scale approach or scoring system which incorporate the actual level of CTC may better discriminate prognosis. These findings, together with the continuum of genetic alterations, support the hypothesis that pPCL represents the extreme end of a biological spectrum rather than a separate disease entity.

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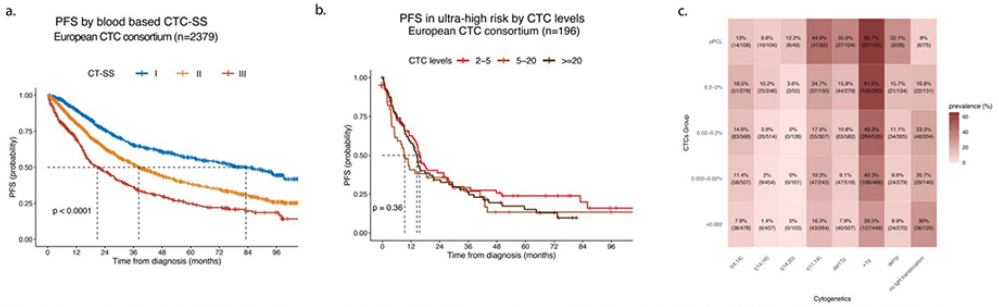
Figure 1



(a) Kaplan-Meier curves showing PFS categorizing patients using blood-based staging system (CTCSS), which includes CTC levels, LDH and ISS patients; (b) Patients with CTC 2-5% have similar outcome to those with CTC - 5-20% and ≥20% (pPCL) in the European CTC consortium. (c) prevalence of specific genetic alteration by FISH increases with CTC levels [e.g. t(11;14), t(14;16), del17p], whereas absence of IgH translocation is less common with increasing CTC levels
Abbreviations: CTC, circulating tumor cells; LDH, lactate dehydrogenase; CTC-SS, CTC staging system; ISS international staging system; pPCL, primary plasma cell leukemia; FISH, fluorescence in situ hybridization.