Identifying Circulating Tumor Cells via Advanced Flow Cytometry as Emerging Prognostic Indicators in Patients with Asymptomatic Monoclonal Gammopathies

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Introduction

Monoclonal gammopathy of undetermined significance (MGUS) and smoldering multiple myeloma (SMM) are precursors to symptomatic multiple myeloma (MM) but exhibit considerable variation in their clinical progression. At present, no single molecular or clinical marker definitively advises immediate treatment, so vigilant monitoring is still the norm; clinical biomarkers like serum free light chains (FLCs), bone marrow biopsy infiltration, and M-protein levels are utilized to gauge the risk of progression. Circulating tumor cells (CTCs), which are clonal plasma cells, are found in numerous patients with symptomatic MM and have independent prognostic value. Employing next-generation flow cytometry (NGF) effectively evaluates CTCs and offers a noninvasive means of monitoring tumor cells. The prognostic importance of CTCs as a biomarker for SMM and MGUS has been infrequently studied. Here, we present findings from a prospective assessment of CTCs, detected with NGF, in patients with SMM or MGUS to establish their prognostic relevance.

Methods

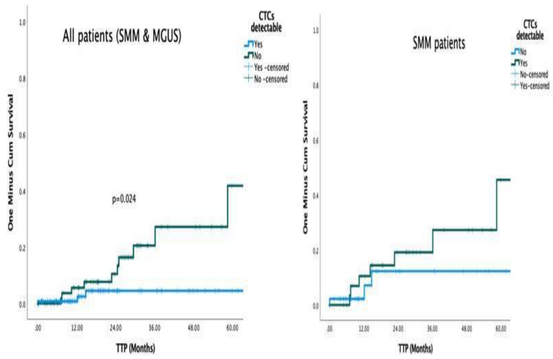
We reviewed data and outcomes for 254 consecutive patients diagnosed with MGUS or SMM following the International Myeloma Working Group (IMWG) 2014 criteria, managed at the Department of Clinical Therapeutics in Athens. Patients underwent prospective CTC detection at initial diagnosis, with assessments in peripheral blood as per EuroFlow guidelines using two independent eight-color panels. These included markers such as CD19-PC7, CD27-BV510, CD38-FITC, CD45-PerCPCy5.5, CD56-PE, CD138-BV421, and additional markers unique to surface or intracytoplasmic tubes. Each tube captured a median of 5 million events, with a median limit of detection of 2.3×10^{-6}.

Cohort

The cohort had a median age of 65 years (range, 28–87), with women comprising 60%. Of the patients, 46.5% had non-IgM MGUS, and 53.5% had SMM. The isotype was IgG in 83% and 74%, IgA in 16% and 22%, and light chain only in 1% and 3% of MGUS and SMM patients, respectively. Among MGUS patients, 46% presented with an abnormal FLC ratio, with a median M-spike of 0.59 g/dL. In SMM patients, 17% had an FLC ratio exceeding 20, 13% had an M-protein spike over 2 g/dL, and 29% had bone marrow plasma cell infiltration over 20%. Based on IMWG's 20/2/20 model, 42% of patients were low (no risk factors), 32% were intermediate (one risk factor), and 11% were high risk (two to three factors). Cytogenetic data from 60 patients revealed specific abnormalities such as t(4;14) in 10% of SMM, t(11;14) in 22%, and
other notable genetic markers.

Findings

CTCs were identified in 39% of patients: 24% with MGUS and 52% with SMM (*P*<0.001). The median CTC level was 0.0019% and showed no significant difference between MGUS and SMM. Detecting CTCs was linked to higher bone marrow infiltration (*P*<0.001) but did not correspond with the SMM risk group, with similar detection rates across low-, intermediate-, and high-risk SMM groups. After a median follow-up of 24 months, the overall 2-year progression rate to symptomatic MM was 9%, with specific rates of 2% for MGUS and 12% for SMM patients. Presence of CTCs indicated a heightened progression risk in the cohort (hazard ratio, 2.99).



Discussion

CTCs are detectable in approximately 39% of asymptomatic monoclonal gammopathy cases, appearing in 24% of MGUS and more frequently, 52%, in SMM. Their presence correlates with an increased risk of progression to symptomatic disease, though ongoing monitoring is essential to clarify their role in MGUS and how they add value to current risk assessment methods. Repeated evaluations may unveil additional prognostic insights. CTCs could offer a simple, noninvasive biomarker for regular patient surveillance.

References

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