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Letter to the Editors

Levels of CD8+ tumor infiltrating lymphocytes correlate with disease burden in bone marrow of therapy Naïve multiple myeloma patients

Dear Editor,

Risk assessment in multiple myeloma (MM) has evolved over time. Earlier models were based on tumor burden and clinical features [1,2]. Subsequently, cytogenetic and molecular data were included in these systems [3,4]. However, with new immunotherapy agents the role of the tumor microenvironment has been increasingly recognized [5]. We assessed CD8+ tumor infiltrating T cells (TILs) in BM of MM and smoldering myeloma (SMM) patients as a potential biomarker.

The study group included 9 SMM (median follow-up 25 months [range, 0–55]) and 25 MM (median follow-up 32 months [range, 0–56]) patients (Table 1). At last follow up, 4 MM patients had died and the others were alive. BM biopsy sections of 34 newly diagnosed MM or SMM were assessed using immunohistochemistry for CD8 (Thermo Scientific, MS-457s), and BCMA (Abcam, Ab5972) and automated image analysis was performed as described [6]. Clinical data were collected from the medical records.

The median CD8+ TILs was 10% in both the MM (range, 2–30%) and SMM (range, 2–20%) groups. Pearson correlation analysis found a negative linear correlation between the CD8+ TILs percentage and the serum paraprotein level in the MM ($r = -0.417$, $p = 0.0377$) but not the SMM groups (Fig. 1).

In MM, 9/22 (41%) patients harbored ≥1 adverse molecular abnormality: 6 *CKS1B* gain, 5 *RB1* loss, 2 *IGH/FGFR3*, 1 *TP53* loss, and 1 *CDKN2C* loss. No correlation was found between the CD8+ TIL levels and these adverse markers. In SMM, 5/9 (55%) patients harbored adverse molecular abnormalities: 5 *CKS1B* gain, 2 *RB1* loss, 1 *CDKN2C* loss. Four of 5 SMM patients had < 10% CD8+ TILs and 1 had > 10% CD8+ TILs ($p = 0.0476$).

No correlation was found between CD8+ TILs and end-organ damage or plasma cell morphology. PCs showed strong expression of BCMA in 32/34 cases (median, 80%).

Others have shown that specific T cells active against tumor antigens correlate with the serum paraprotein level in MM [7]. We also found a correlation between CD8+ TILs in BM and paraprotein levels. These results support the role of immune microenvironment in myeloma biology. We also show that BM CD8+ TILs at baseline may control tumor burden (paraprotein) and suggest that CD8+ TIL counts may identify a more immunogenic disease or more effective response.

High risk SMM is currently defined by clinical parameters. [8,9] The integration of molecular and immune markers remains elusive. Paiva et al. evaluated peripheral blood T cells by flow cytometry in high-risk SMM patients and described normal absolute numbers and relative distributions of CD4 and CD8 cells [9,10]. Willenbacher et al. reported that BM CD8+ TILs in MM correlate with survival [5]. We show that BM CD8+ TILs < 10% may identify patients who harbor adverse risk abnormalities in SMM patients, suggesting that direct assessment of BM is valuable.

In summary, we identified a negative correlation between CD8+ TILs and paraprotein levels in therapy naïve MM patients. BM CD8+ TILs < 10% correlate with adverse molecular makers in SMM. These results provide a basis for prospective studies to validate the utility of immune markers in MM.

Table 1
Clinicopathological characteristics of study group.

Characteristics	SMM	Naïve MM	
No. of patients	9	25	
Median age			
Years	66	65	
Range	47–79	40–75	
Gender, ts (%)			
Women	4 (45)	6 (24)	
Men	5 (55)	19 (76)	
End organ damage, pts (%)*			
Hypercalcemia	–	6 (24)	
Renal insufficiency	–	12 (48)	
Anemia	–	20 (80)	
Bone lesions	–	14 (56)	
International score system		ISS	R-ISS
1	–	14	11
2	–	7	7
3	–	4	7
Serum M-component, g/24 h			
Median	1.7	3.3	
Range	0.5–4.3	0–5.2	
Plasma cell morphology WHO 2016, (Pts)			
Mature	4	8	
Immature	5	17	
Plasmablastic	0	0	
BM biopsy PC infiltration CD138, %			
Median	20	50	
Range	10–60	15–90	

Pts: Patients. ISS: International score system. R-ISS: Revised International score system. WHO: World Health Organization classification. BM: Bone marrow. PC: Plasma cells.

* Hypercalcemia: serum calcium > 0.25 mmol/L (> 1 mg/dL) higher than the upper limit of normal or > 2.75 mmol/L (> 11 mg/dL). Renal insufficiency: creatinine clearance < 40 mL per minute or serum creatinine > 177 μmol/L (> 2 mg/dL). Anemia: hemoglobin value of > 2 g/dL below the lower limit of normal, or a hemoglobin value < 10 g/dL. Bone lesions: one or more osteolytic lesions on skeletal radiography, computed tomography (CT), or positron emission tomography-CT (PET-CT).

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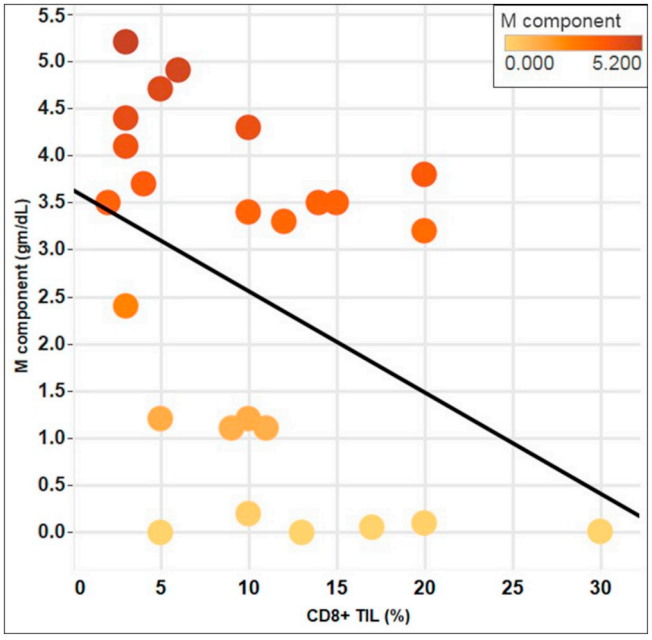

Fig. 1. Negative linear correlation between CD8+ TIL (%) and monoclonal component (gm/dL) ($r = -0.417$, $p = 0.038$).

Conflict of interest

The authors declare that they have no conflict of interest.

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