Monocytes, Monocytic Myeloid Derived Suppressor Cells and Lymphoma: How Tight is the Knot of the Tie?

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Much effort is being invested in advancing the knowledge on cancer immunology, cancer microenvironment, and their interactions both within and outside the tumor niches. In the past few years it has been recognized that tumor growth and progression, do not depend only on the biology of the malignant cells themselves but also on their interactions with a variety of other cells which play a central role in tumorigenesis [1].

Until recently, most of the experts in the field of cancer immunology could indeed be considered as “T-cell chauvinists”- as their main research interests focused on improving adoptive T-cell transfer, understanding “T-cell anergy” in cancer, and inhibiting T-regulatory cells (T-regs), a sub-population of T-cells with immunosuppressive activity. This has still remained so, until now and in the hierarchy of the cancer involved immune system, T-cells and their related subpopulations still reign supreme [2]. However, other immune cells are now being investigated and new immunosuppressive sub-populations have been discovered, including the T17, B- regulatory cells (B-regs), Myeloid Derived Suppressor Cells (MDSc) and some dendritic and natural killer cells [3,4]. Understanding their functions and interaction with tumor cells and other immunosuppressive and immune-active populations is important when trying to understand more clearly the “full picture” of tumor-immune tolerance.

In recent years, we have been interested in the role of peripheral blood monocytes in lymphoproliferative disorders in general and in lymphomas in particular, and have investigated them as a possible surrogate prognostic marker for patients with lymphoma. When we analyzed the numbers of monocytes in the peripheral blood of patients with diffuse large B-cell lymphoma treated in our institute, we observed that high monocyte numbers correlated with adverse prognosis in these patients [5]. Together with the “Gruppo Italiano Studio Linfomi” we then validated our initial results in a large cohort of 1191 patients, and identified monocytes >630 mm³ as a cut-off value of adverse prognosis [6]. Our results are in similar to those of other groups working in this field, particularly those at the Mayo clinic, in Rochester, Minnesota demonstrating in a multivariate analysis that the Absolute Monocyte Count (AMC) was as an independent prognostic marker, with an HR as significant as the IPI [6,7]. A similar retrospective analysis was performed by our combined Israeli-Italian groups, involving a cohort of patients with T-cell lymphomas [8] and Hodgkin disease [9] where we once again confirmed, the role of AMC as a simple and applicable prognostic marker in lymphomas, where patients with elevated AMC had a significantly less favorable prognosis [10].

Furthermore the prognostic value of AMC was also examined and reported by other groups not only in lymphomas, but also in other hematological disorders such as idiopathic myelofibrosis [11], and non- hematologic malignancies, including head and neck cancer, renal cell carcinoma, and melanoma [12,13] and Similar conclusions as for lymphomas were drawn in all these studies.

Monocytes are produced by the bone marrow, and in response to inflammatory signals, migrate to the blood and to sites of infection where they differentiate into macrophages and dendritic cells and elicit an immune response [14]. However in vitro studies demonstrated that their functions are not limited only to immune-defense, Monocytes are indeed a heterogeneous population, including a sub-population with immune-suppressive activity termed: Monocytic-Myeloid Derived Suppressor Cells (M-MDSc). These cells elicit their immunosuppressive activity utilizing different mechanisms and one of the best recognized of these is via arginase secretion which induces depletion of arginine in T-cells surrounding and in consequence T-cells are unable to generate the zeta chain and mature into active cytotoxic T-cells. The second important pathway is dependent on inducible nitric oxide synthase 2 (iNOS2). Phenotypically, monocytes are characterized being both CD14 positive/HLA DRr low/negative and mostly D16 negative and CD66b positive [15]. In our laboratory, we have examined the presence and percentage of M-MDSc in the peripheral blood of newly diagnosed patients with DLBCL. When compared to normal controls, patients with DLBCL had a statistically significant higher percentage and absolute number of peripheral blood M-DSCs at the time of diagnosis. Interestingly, when we evaluated these cells at the end of therapy, we demonstrated that the number of M-MDSc decreased to values similar to those of healthy controls [5]. In 2011, Lin et al. [16], performed the first pioneering in vitro study evaluating the mechanism in which monocytes affect the growth of non Hodgkin lymphoma cells. Monocytes had a suppressive effect on T-cell function, which was mediated through arginine metabolism, and indeed when exogenous arginine was added, this suppressive effect was over. Taking all the above into consideration, we can conclude, that it is becoming more and more evident, that the absolute monocyte count serves as a simple prognostic parameter in lymphoma, and AMC will probably be used more frequently by clinicians in the future. Studies are now in progress attempting to better understand the biological mechanisms used by monocytes and which affect their suppressive function.

References


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