Evaluation The Role of CD33+ CD11b+ myeloid-derived Suppressor Cells in Patients With AML

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ABSTRACT
Acute myeloid leukemia is a genetically heterogeneous clonal disease defined by the accumulation of immature cells in bone marrow and blood. The aim of this study is to evaluate the CD33, CD11b, and HLA-DR expression in Iraqi AML patients and its role in evasion of malignant cells from the immune system. This study was conducted on 60 patients with AML and 20 healthy individuals as a control group to evaluate the expression of CD33 and CD11b using flow-cytometry in peripheral blood, and evaluate Interferons-γ (IFN-γ) and Transforming Growth Factor-β1 (TGF-β1) levels. A statistically non-significant difference (P < 0.005) between the AML patients and control group with regard to the expression of CD33, CD11b, and HLA-DR was observed. Analysis of CD33 expression in myeloid-derived suppressor cells (MDSCs) showed a significant decrease in the proportion of CD33 positive MDSC cells in isolated peripheral blood samples (88.078 ± 1.284). Also, the expression of CD11b in MDSC cells was high (98.841±1.935) in MDSC cells. The mean level of IFN-γ (pg/ml) increased in AML in compared to control group (9.202 ± 0.244), (7.906±1.22), respectively. While TGF-β1 (pg/ml) concentration was found to be elevated in AML patients (69.04 ± 9.92) compared to control group (33.884 ± 2.888). In conclusion, circulating MDSCs were significantly elevated in peripheral blood of patients with AML and characterized by the CD33+CD11b + phenotype; TGF-β1 and IFN-γ can be released in the presence of native human AML cells and affect AML cell proliferation and evasion from immune system.

Keywords:
CD11b.
CD33.
HLA-DR.
MDSC.
AML.

1. Introduction
About 25 percent of adults in the Western world have acute myeloid leukemia (AML), which is a medically and molecularly inhomogeneous disease [1]. Undifferentiated myeloid cells accumulate in the bone marrow and propagate in high proportions in AML, which is a form of cancer. In healthy bone marrow, the proportion of blasts is 5%. There is a much larger proportion of AML patients (at least 20%) [1].

It is possible to describe the tumor microenvironment (TME) as essentially being that of the tumor’s cellular exterior. A wide range of cells, including endothelial and immune cells, make up the TME, which plays a major role in the development and spread of cancer in general, as well as influencing the efficacy of different cancer treatments [2]. Oncologists have documented TME from several hematologic malignancies, including Hodgkin Lymphoma (HL), acute lymphoblastic leukemia (ALL), chronic myeloid leukemia (CML), and chronic lymphocytic leukemia (CLL), but AML has remained poorly studied to date [3]. Several studies have shown that AML can affect the
immune system in a variety of ways to create a favorable environment for the growth of AML [4].

As a means of preventing an immune response, cancerous cells reduce the activity of immune system while also selectively triggering cells with immunosuppressive processes, such as inoperable dendritic cells, regulatory T (Treg)-cells, and malignant macrophage cells. These include myeloid-derived suppressor cells (MDSCs), which are obtained from premature myeloid cells that originate from hematopoietic stem cells (HSCs) and are thus generated in certain circumstances [5].

T-cells, as well as natural killer cell respondents in tumors, are suppressed by MDSCs. The MDSCs also produce Treg cells, which are also implicated in immnosuppression, fostering tumor growth, and distant metastasis [6]. MDSC accumulation has been implicated in tumor-associated immunosuppression in series of studies, which is a phenomenon common to most forms of cancer [7]. Decreased survival rates and malignant tumors are also associated with higher MDSC levels [8]. The involvement of MDSCs and their immunomodulatory feature in hematologic malignancies has been confirmed by a vast number of studies; however, the exact phenotype and accompanying pathway associated with this immunosuppression are still unknown. This was demonstrated in a recent study into multiple myeloma mononuclear MDSCs (CD11b+, CD14+, HLA-DR/low) and bone marrow MDSCs (BM-MDSCs) (CD11b+, CD14, CD33+, and CD15+) from the BM [9].

AML’s beginning and development might be influenced by MDSC-specific immunosuppressive capabilities. AML patients’ bone marrow has been examined to determine whether CD11b+ CD33+ HLA-DR- MDSC-like blasts with much the same genetic makeup as MDSC were present in the BM, and whether these cells had immunosuppressive functions that promoted leukemic cellular proliferation. They express CD33 and CD14 (monocytic MDSC) or CD15 (multinucleated MDSC) (neutrophilic MDSC). Staf-3 (STAT3) is phosphorylated by interferon-gamma, which leads to the creation of indoleamine 2-3 dioxygenase (IDO), arginase (ARG1), as well as nitric oxide. T-cell activation, multiplication, and cytoxicity are all inhibited by MDSC through these dissolved intermediaries, and that both T- and NK cells become anergic. A growing body of evidence indicates that MDSCs play an important role in the immune avoidance strategy of many malignant tumors. Also, MDSCs are implicated in AML's immune modifications [10]. In current study we aimed to determine the presence of Myeloid derived suppressor cells (MDSC) that causing the immune suppression and to evaluate TGF-β1 and IFN-γ levels in serum.

2. Methods and Procedures

2.1. Participants

Subjects and methods

This prospective cross-sectional study was conducted on Iraqi patients with AML in the Hematoloy center, Baghdad Teaching Hospital, Medical City. This study included 60 patients diagnosed with AML, and 20 healthy individuals as a control group with matching ages and sexes.

2.2. Samples collection:

Blood was collected aseptically by venipuncture and distributed into two parts, one part was transferred into a sterile blood collection tube with a dipotassium ethylene diamine tetra-acetic acid (K2EDTA) vacutainer, whilst the other part was transferred into a gel tube to obtain serum.

2.2 Flow cytometer analysis of membrane molecule expression

Membrane molecule expression was analyzed via flow cytometry (FCM) using PE, APC, PerCP, and FITC-conjugated anti-CD11b, CD33 and CD45 as gating monoclonal antibodies, respectively (Elabscience Biotechnology Inc, United States). The data were analyzed on a flow cytometer using BD FACS Canto with FACSDIVA software into the flow cytometer [11].

2.3 IFN-γ and TGF-β1 measurement

For IFN-γ (pg/ml) and TGF-β1 (pg/ml) measurements, SUNLONG BIOTECH Co., LTD/China provided sandwich ELISA reagent kits. Both IFN- and TGF-β1 standard curves were established using appropriate recombiant human protein. This was carried out in accordance with the manufacturer's instructions. Using a standard curve, IFN- and TGF-β1 concentrations were determined.

2.4 Ethical approval

All investigations were performed in accordance with the Al-Anbar University Medical Research Ethics Clearance Committee guidelines, University of Anbar, Anbar, Iraq. The local ethics committee approved (Ref: 192 Date: 19/1/2020) the study protocol and informed consent was obtained from all subjects.

2.5 Statistical Analysis:

Numbers were presented as minimum and maximum values, as well as a mean and median and standard deviation
different AML patients were examined for CD33, CD11b, and HLA-DR expression. Standardized fluorescence intensity (SFI) was used as a readout because the mean fluorescence intensity showed a large range in the expression of the CD markers (MFI). We evaluated the clinical relevance of circulating CD33+ CD11b+ HLA-DR- MDSCs in patients with AML in whole-blood samples using flow cytometry. Peripheral blood samples of AML patients were analyzed at different time points, before and following treatment and also at different age stages compared them with healthy people. It was found that circulating MDSCs frequencies of AML were significantly higher in the group of patients diagnosed with AML for 1 month to 1 year (22.941±3.81) than those of the newly diagnosed group (15.333±2.12) and the patients who diagnosed for more than a year (17.000±5.92). However, there were a significant statistical increase (p≤0.05) in circulating MDSCs in males (29.0588±3.25) comparing to females (22.3043±2.63) in AML patients. The proportion of MDSC in patients after chemotherapy was higher (19.500±3.8) in comparison to newly diagnosed patients (15.333±2.12).

We first assessed constitutive MDSCs cell surface CD33 protein expression via flow cytometry. Analysis of CD33 expression in MDSCs populations showed a significant decrease in the proportion of CD33-positive MDSCs cells in isolated peripheral blood samples of AML patients (88.078 ± 1.284) compared to the control group (93.7000 ± 0.57170). When comparing the SFI of CD33 on freshly isolated MDSCs cells from male patients with MDSC cells isolated from female patients, no significant differences were observed (93.881 ± 1.851; 92.655 ± 1.773, respectively). For duration since diagnosis, the first group (non-treated, recently diagnosed) CD33 expression was 95.6667 ± 1.08252, whilst for the second group (duration between 1 month to 1 year) CD33 expression was 88.3529 ± 3.56034, and for the last group (more than one year), CD33 expression was 82.5000 ± 8.35165. We noted that there was a non-significant decrease in CD33 expression with increasing duration of having the disease and exposure to treatment (Figure 1).

### 3. Results

#### 3.1 Baseline characteristics of included patients

The present study was conducted on 60 patients with AML and 20 healthy individuals collected from the Haematology center, Baghdad Teaching Hospital, Medical City. Out of 60 participants, 24 were male and 36 females, with 20 controls (10 males and 10 females). The mean age of patients was 45.8 years, with an age range from 13 to 70 and a control group mean age of 32.4 years, with an age range from 18 to 70. According to duration of the disease, the patients were divided into three groups, where 39 (65%) were newly diagnosed with AML (non-treated), 17 (28.33%) had been diagnosed between one month and one year previously, and 4 (6.67%) had been diagnosed for more than one year (Table 1).

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#### 3.2 Flow Cytometer Data

Assessment of MDSC cells markers’ expression in AML patients

At different treatment time points, leukemic MDSC cells from the freshly isolated peripheral blood samples of
3.3 Frequency of CD11b gene expression

The percentage of CD11b expression on MDSCs cells in AML was very high (98.841±1.935), compared to control group (92.966±1.145). The proportion of CD11b expression on MDSC cells the mean ± SD was significantly increased in the female (98.60 ± 1.07497) compared to male (94.8750 ± 1.145) population. With regard to the time period, we noted that the expression increased as the disease progressed in time when comparing the newly diagnosed group (91.7667 ± 1.67538) with the patients whose duration ranged from one month to one year (93.3941 ± 2.15008), as well as with the patients who had been infected for more than one year (99.2750 ± 0.42303) (Figure 2, table 2). MDSCs were negative for HLA-DR.

3.4 IFN-γ and TGF-β1

In the present study, the mean level of IFN-γ (pg/ml) was non-significantly increased in AML compared to the control group (9.202 ± 0.244 and 7.906±1.22, respectively) (Figure 3). With regard to the effect of gender, IFN-γ (pg/ml) was non-significantly increased amongst the male (9.414 ± 0.93) compared to the female (9.054 ± 0.81) in AML patient populations. When we compare the effect of treatment, we find that the concentration of IFN-γ (pg/ml) decreased insignificantly in treated patients compared to newly diagnosed patients (9.2975 ± 0.29 and 9.192 ± 0.3, respectively).

TGF-β1 (pg/ml) concentration elevated significantly (P ≤ 0.05) in AML patients (69.0344 ± 3.91) compared to the control group (33.884 ± 2.888). It is obvious that TGF concentration elevated significantly (P ≤ 0.05) in males (78.0588 ± 12.472) compared to the females (61.7826 ± 11.945) in the AML group. While the duration effect of the concentration of TGF was significant (71.0473 ± 2.58) in the newly diagnosed patients. It was (72.4089 ± 4.028) for patients diagnosed with AML for more one month and treated with chemotherapy and (35.0679 ± 10.56) for those who had had the disease for more than one year, (Figure 4).
found to repress hematological malignancies versus solid tumors. Therapeutic administration. As seen in
abuse only bidirectional. This matches previous studies when comparing as repeatedly demonstrated that
Control these MDSCs play a role in AML cellular
14+ monocytic MDSC levels CD11b and HLA
AML. Our results agree with previous research [13] in which MDSC’s capacity to reduce T
HLA
patients' blood, MDSC showed greater CD11b, CD33, and proliferation. Unlike the other blast populations found in AML
patients' blood, MDSC showed greater CD11b, CD33, and HLA-DR expression, indicating that they play a role in
MDSC's capacity to reduce T-cell proliferation, but removal of these cells recovered this activity [15]. The current study found that in
AML, there is a blast subpopulation that shares the phenotypic and immunosuppressive effects of MDSCs. Pyzer et al. identified CD11b+, HLA-DR-, CD14, CD33+, and CD15 to be monocytic MDSCs and CD11b+, HLA-DR-, CD14, CD33,
and CD15+ to be granulocytic MDSCs, respectively, among PB MNCs from AML patients using flow cytometry [16]. Their findings revealed that MDSCs were present in 7.9% of AML patients’ PBs, and that co-culturing an AML cell line with PB monocytes from a healthy person resulted in MDSC proliferation, implying that MDSC levels rise as AML progresses. Sun et al. also measured CD33+, CD11b+, and HLA-DR- cells in BM in AML patients, finding that there were more CD33+, CD11b+, and HLA-DR- monocytic MDSCs [17]. CD33 is also one of the antigens that is commonly expressed in AML. We found that CD33 expression in MDSC populations showed a significant decrease in the proportion of CD33 positive MDSC cells, which is in agreement with previous results [13]. CD33 expression is limited to initial multi-lineage hematopoietic progenitors, myelomonocytic antecedents, and much more matured myeloid cells in a physiological sense, with normal undifferentiated hematopoietic stem cells being devoid of it. The CD33 antigen is present in 85-90 percent of AML
patients. As a result, CD33 has gained clinical significance as a tumor-associated antigen and as a target for antibody-based AML treatments [18]. Finding out how much CD33 is expressed on the membrane of AML cells could have clinical ramifications. A higher antigen production intensity means a higher therapeutic antibody affinity and, as a result, better conjugated chemotherapeutic administration. As seen in patients with acute promyelocytic leukemia, cells with a higher CD33 density have a higher chance of catching and internalizing anti-leukemic drugs [19].

4. Discussion

With multicolor FCM, the transcription properties of lineage cluster CD indicators in hematopoietic cells have indeed been successfully and broadly employed for the study and isolation of various blood cells [12]. MDSCs are immature myeloid cells that have been found to repress immune responses and proliferate during cancer, infection, and inflammatory disorders. Despite the fact that MDSCs have received a lot of interest in the field of tumor immunology in recent years, less is known about their varied roles in hematological malignancies versus solid tumors. There have been a few studies into MDSCs in leukemia, especially for AML. The results of the current study showed that the level of cells that were positive for immune parameters (CD11b+, HLA-DR-, CD33+) was very high (figure 3). This matches previous studies when comparing MDSCs (CD11b+, HLA-DR-, CD33+, Lin-) in the PB and BM of AML patients to healthy donors, where more MDSCs (CD11b+, HLA-DR-, CD33+, Lin-) were found in the PB and BM of AML patients [10]. Because only bidirectional regulators were involved, the interaction between MDSCs as well as the tumor microenvironment was rather basic. We found that CD11b+, CD33+, and HLA-DR- MDSC exist in different numbers in the peripheral blood of patients with AML, and these MDSCs play a role in AML cellular proliferation. Unlike the other blast populations found in AML patients' blood, MDSC showed greater CD11b, CD33, and HLA-DR expression, indicating that they play a role in MDSC's capacity to reduce T-cell-specific immune activity in AML. Our results agree with previous research [13] in which it has been found that MDSCs characterized with CD33+, CD11b and HLA-DR low/-. These MDSC-like blasts, as hypothesized, had an impact on prognosis, with worse survival rates in patients with high percentages of MDSC-like blasts, especially those who did not receive allogeneic HSCT. This research suggests that the presence of MDSC-like blasts in the BM at the initial diagnosis may be a prognostic factor in AML. Previous research has repeatedly demonstrated that MDSCs in the peripheral blood contribute to the advancement of various malignancies by suppressing T-cell response through the production of iNOS, ARG1, and inflammatory cytokines [14]. MDSCs are immature myeloid cells that can be further divided into two groups: granulocytic (CD11b+, CD33+, CD14, HLA-DR-/low) and monocytic (CD14+HLA-DR-/low). MDSCs were found in the peripheral blood of patients with widespread large B-cell lymphoma. Azzouei et al. discovered that elevated CD14+ monocytic MDSC levels reduced T-cell proliferation, but removal of these cells recovered this activity [15]. The current study found that in AML, there is a blast subpopulation that shares the phenotypic and immunosuppressive effects of MDSCs. Pyzer et al. identified CD11b+, HLA-DR-, CD14, CD33+, and CD15 to be monocytic MDSCs and CD11b+, HLA-DR-, CD14, CD33,
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![Figure 4 TGF-beta1 (pg/ml) between groups. TGF concentration elevated significantly (P ≤ 0.05) in males (78.0588 ± 12.472) compared to the females (61.7826 ± 11.945) in the AML group.](image-url)
that AMLs with NPM1 mutations exhibit significantly higher levels of CD33 antigen expression, suggesting that this finding could have therapeutic consequences for this critical subgroup of AML patients [20]. CD33 is detected on myeloid-lineage cells, myeloid leukemia blasts, and mature monocyes, but not on normal immature hematopoietic stem cells [18]. CD33 is a cell-surface biomarker that has previously been used to diagnose AML [21][22][23]. However, its activation on AML cells, as well as those from other MDSs and MPDs, has not been quantified. When patients are treated with a regimen that incorporates an anti-CD33 drug, the evaluation of the level of CD33 production on the surfaces of cells may well have clinical implications. Cells with a higher CD33 intensity should theoretically have a better probability of catching anti-CD33 agents, the antibody, and conjugating therapies [24].

MDSC that were CD33+ or CD11b+ had immature myeloid appearance, poor HLA-DR expression, and lacked lineage matured surface markers. MDSC blocks T-cell effector responses via a variety of mechanisms and both the CD33+ and CD11b+ subtypes of MDSC demonstrated up-regulation of classical suppressive mechanisms (ARG-1, iNOS, NOX2). Previously, it has been shown that distinct cytokine mixes associated with actively suppressive function caused modest differences in the patterns of repressive genes that were slightly higher than those in human myeloid suppressor cells [25]. Elevated CD33+ MDSCs have been discovered in tumor microenvironments, which are typically associated with a poor prognosis [26]. Furthermore, CD33+ MDSCs were distinct determinants, and their density had predictive significance for cancer patients, whether they were in the early or late stages of the disease. CD11b is a prognostic marker for neutrophil engangement and is important for cellular proliferation and migration [27]. Integrins, such as CD11b, have been linked to tumor resistance, cellular connections, and microenvironmental involvement [28][29].

When the mean level of IFN-γ (pg/ml) is non-significantly decreased in AML when T-cells are stimulated in the presence of original human AML cells and bone marrow-derived cells, IFN γ is produced. The release of various immune-regulatory cytokines by indigenous human AML cells is constant, which can have an antigen-nonspecific influence on the production of IFN γ by activated T-cells. The amount of constitutive release varies depending on the subject [28]. Several transmembrane molecules implicated in immunological recognition, such as HLA-class II (particularly HLA-DR), CD40, CD54, CD80, and probably CD83, have been shown to boost the expression of IFN γ in AML cells in previous investigations [29]. Taken together, these findings clearly indicate that local IFN γ secretion is a component of antileukemic T-cell responses and clinical investigations of IFN γ therapy have shown that IFN γ has physiological activities on human AML cells [30]. On the other hand, TGF-β1 (pg/ml) concentration elevated significantly. Many cellular activities, such as proliferation, transformation, migration, and cell survival are controlled by the TGF-signalling pathway. A potent negative modulator of cell proliferation throughout hematopoiesis, the TGF-β1 signaling pathway stimulates differentiation and death when necessary [30]. On the mammalian side, TGF-1 is the most plenteous and widely studied isofrom, followed by TGF -β2 and TGF -β3. In humans, TGF-1 is abundant in platelets [31]. Bioactive TGF- is secreted as a dormant protein complex that must be activated. Type I (TRI) and type II receptors (TRII) contain serine/threonine protein kinase in intracellular domains, allowing TGF ligands to start regulating cellular processes once activated. After binding TGF-1, TRII recruits, binds, and transphosphorylates TRI, enhancing its protein kinase activity [31]. It then recruits Smad2/3 receptor-activated transcription factors, which bind to Smad4 and translocate into the nucleus, where they interact in a cell-specific manner with transcription factors (e.g., Runx1, E2F), coactivators (c-Ski, SnO, TGF), and corepressors [32]. Resistance to these homeostatic influences of TGF- develop in hematologic malignancies, which include leukemia, myeloproliferative disorders, lymphomas, and multiple myeloma. Mutations or deletions of members of the TGF- signaling pathway, as well as disruption of the pathway through oncoproteins, all contribute to this resistance. The TGF- pathway plays a tumor-suppressing role in human hematologic malignancies as a result of these alterations. Due to its effects in both the stroma and the immune cells, elevated levels of TGF- can also contribute to myelofibrosis and certain hematologic malignancies [33].

5. Conclusion

Over all our study found that CD33, CD11b expression, and immune evasion in AML were all shown to be associated with one another and with MDSC escape from the immune system. TGF-β1 and IFN-γ play an important role in the TME as a part of the complex immune response to cancer.

6. References


تقدير دور الخلايا المثبطة MDSC لدى مرضى 

CD33 و CD11b

ابيضاض الدم النقياني الحاد

الخلايا المثبطة MDSC لدى مرضى MDSC

الخلايا المثبطة MDSC

الخلايا المثبطة MDSC

الفحص:

هو مرض وراثي غير متضمن يتم تشخيصه من خلال وجود وتروك الخلايا الأورومية غير الناضجة في نخاع العظام والدم المحيطي. هذه الدراسة تحقق من تأثير علاج CD11b و CD33 في مرضى AML في مرضى MDSC في مرضى MDSC. وجدت الدراسة أن CD33 و CD11b تتأثر بشكل واضح عند المرضى الذين تلقوا العلاج عن المرضى الذين لم يتلقوا العلاج. الاشخاص الذين تلقوا العلاج تأثر باستخدام MDSC بشكل واضح. الاشخاص الذين لم يتلقوا العلاج تأثر باستخدام CD33 بشكل أقل واضح. الاشخاص الذين تلقوا العلاج تأثر باستخدام CD33 بشكل أقل واضح. الاشخاص الذين لم يتلقوا العلاج تأثر باستخدام MDSC بشكل أقل واضح.

لدى مرضى MDSC في المرضى الذين تلقوا العلاج، وجدت الدراسة أن CD33 و CD11b تتأثر بشكل واضح عند المرضى الذين تلقوا العلاج عن المرضى الذين لم يتلقوا العلاج. الاشخاص الذين تلقوا العلاج تأثر باستخدام MDSC بشكل واضح. الاشخاص الذين لم يتلقوا العلاج تأثر باستخدام CD33 بشكل أقل واضح. الاشخاص الذين تلقوا العلاج تأثر باستخدام CD33 بشكل أقل واضح. الاشخاص الذين لم يتلقوا العلاج تأثر باستخدام MDSC بشكل أقل واضح.

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