P1255 TUMOR-ASSOCIATED MONOCYTIC MYELOID DERIVED SUPPRESSOR CELLS IS A POTENTIAL PROGNOSTIC BIOMARKER, PROMOTING MULTI-DRUG RESISTANCE IN NHL PATIENTS BY MODULATING IL-6/IL-10/IL-1B AXIS

**Topic:** 20. Lymphoma Biology & Translational Research

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**Background:**

Non-Hodgkin-Lymphoma (NHL), the most prevalent hematologic malignancies in the world has majorly originates from B cells. R-CHOP represents the new-standard treatment regimen for NHL. Most NHL patients initially respond to chemotherapy yielding complete response rates of 40–50%. Unfortunately, a substantial population of patients undergo relapse, resulting in poor clinical ramifications. The onset of NHL relapse evolves from several months (early relapse) to years (late relapse) after the initial remission. However, the majority of relapse occurs within two years of initial treatment. Despite considerable advancements in therapeutic concepts and techniques, disease relapse with limited response rate remains a major challenge and depicts poor prognosis in successful clinical management. Patient’s response to chemotherapy varies widely from static disease to cancer recurrence and the later is primarily associated with generation of multi drug resistance (MDR) phenotypes that ultimately promotes disease progression and metastasis. However, the causes of differential responses to standard chemotherapeutic regimens and therapy failure in NHL patients are yet to be elucidated.

**Aims:**

To understand the influence of immune cells in differential response in NHL patients following R-CHOP-therapy.

**Methods:**

Peripheral blood was collected from 51 CD20+ NHL patients before and after frontline chemotherapy and at the time of relapse. Clinical variables at diagnosis (age, performance status, stage of the disease, number of extra nodal lesions) were obtained to calculate prognostic indices (IPI). A panel of immune cells CD4+ T cells, CD8+ T cells, Cytotoxic T cells, CD8*CD45RO*CD45RA* Memory T cells, CD14*CD80* M1 macrophage, CD4*CD25*FoxP3 regulatory T cells(Treg), CD33*CD11b*CD14*CD15* Myeloid Derived Supressor Cells(MDSCs), CD14*CD163+ Tumor associated Macrophages (TAM), MDR phenotype P-gp(ABC1) and MRP1(ABCC1) were studied by flow-cytometry at different phases of treatment. In vivo and in vitro doxorubicin resistance model were developed with murine Dalton’s lymphoma and Raji (B cell), Jurkat cell (T cell) lines respectively and impact of responsible immune cells on generation of drug resistance were studied by RT-PCR, qPCR, flow-cytometry, colorimetric assay, gene silencing and ChIP assays.

**Results:**

A strong positive correlation between elevated levels of CD33*CD11b*CD14*CD15+ monocytic MDSCs, but not CD33*CD11b*CD14*CD15+ granulocytic MDSC and MDR was depicted in non-responder patients compared to responder cohorts. Moreover, in vitro supplementation of MDSCs in murine or human lymphoma culture increases the expression of mrp1, pgp and cellular GSH level from early passage than passage without MDSCs, which is
correlated well with *in vitro* drug retention and generation of drug resistance phenotypes and tumor progression. MDSC secreted cytokines IL-6, IL-10, IL-1β are the dominant constituent in regulating expression of multidrug-resistance pump by modulating STAT3, STAT1 and NF-κβ signalling axis.

**Summary/Conclusion:**

Observed correlation between monocytic MDSCs with the relapse of NHL patients following R-CHOP-therapy along *in vitro* data from lymphoma cells suggest monocytic MDSCs might be considered as a new potential biomarker and therapeutic target to enhance the relapse free survival in NHL patients.