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Abnormal levels of functional CTLs on high risk MDS patients under azacytidine treatment

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Background

CD3+CD8+ cytotoxic T cells (CTLs) play important role in antitumor immunity. Myelodysplastic Syndromes (MDS) are typically associated by immune dysregulation leading to compromised function of CTLs. The hypomethylating agent azacytidine (AZA) appears to affect the antitumor immune response, therefore we investigated both pretreatment and after treatment levels of functional subsets of CTLs in high-risk MDS patients under AZA treatment and their association with various clinical parameters.

Materials and Methods

Peripheral blood mononuclear cells from 72 patients and 13 healthy donors were obtained before, at Day15 and at the 6th cycle of AZA treatment. According to IWG criteria patients were characterized as responders (complete remission and hematologic improvement, 55%) and non-responders (stable disease and failure, 45%). We utilized various protocols of multiparameter flow cytometry to assess the polarization, differentiation and functional states, by measuring the intracellular levels of Interferon γ, Interleukin 4, the levels of naïve CTLs (TN, CD27+CD45RA+), effector memory (TEM, CD27-CD45RA-), terminal effector memory (TEMRA, CD27-CD45RA+) and central memory (TCM, CD27+CD45RA-) and the levels of perforin, CD57 and program death receptor (PD1+ CTLs).

Conclusion

Collectively, our results demonstrate the CTL-mediated antitumor immune response is defective in high-risk MDS. AZA therapy increased CTL levels independently of response, without affecting their differentiation or functional state. PD-1 expression on CTLs remained unaffected by AZA treatment in all patients but was upregulated in TCM cells of non-responders potentially indicating a link, an undesirable compromise of antitumor immunity with failure to AZA.

Bibliography

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Results

Pretreatment levels of CTLs were decreased in high-risk MDS patients in comparison to healthy controls (p=0.037, figure 1A). MDS patients had also decreased pretreatment levels of perforin+ CTL cells (p=0.045, figure 1B) and increased levels of PD1+ TEMRA CTLs (p=0.019, figure 1C) in comparison to healthy donors.

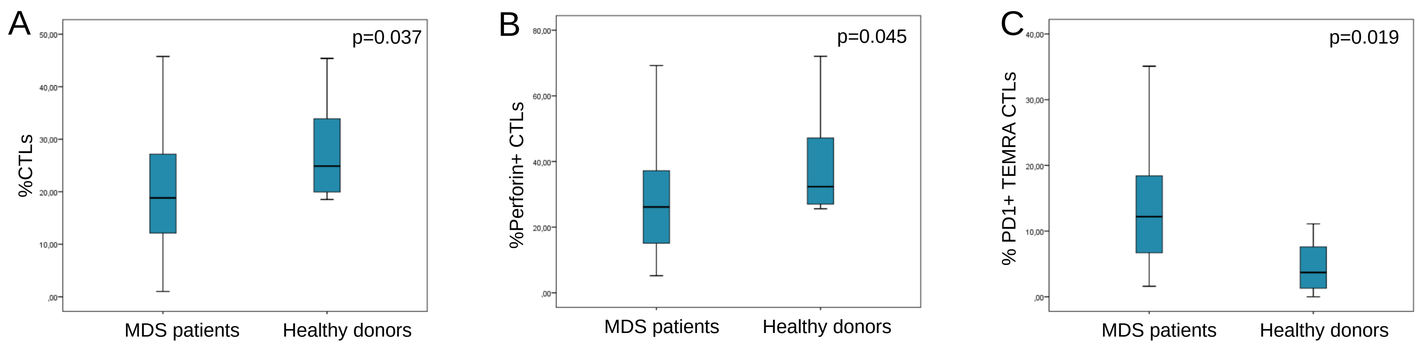

Figure 1. A. CTL levels in MDS patients and healthy donors B. Perforin levels among MDS patients and healthy donors C. The levels of PD1+ TEMRA CTL cells

The levels of perforin+ CTLs were positively associated with the levels of TEMRA CTLs (p=0.041). Also, TEMRA CTL cells had higher levels of CD57 molecule (p<0.001, Figure 2) and lower levels of PD1 (p<0.001, Figure 2) in comparison with TEM, TN and TCM, indicating higher cytotoxic activity of that subset.

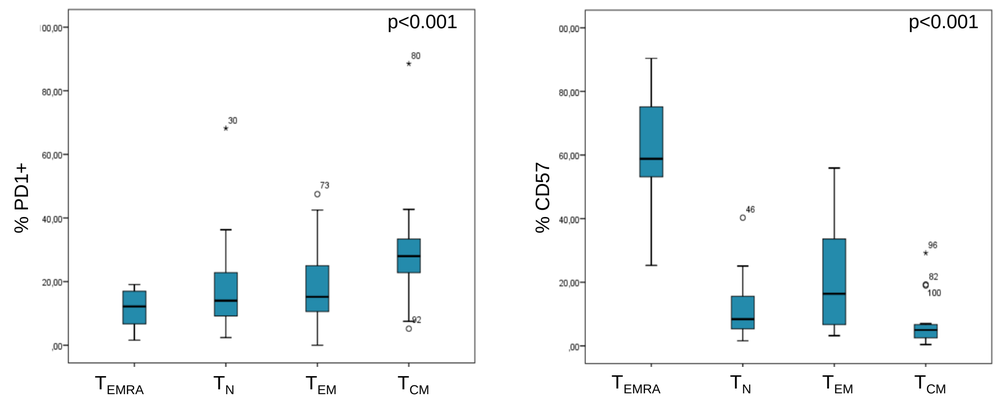

Figure 2. PD1+ CTLs and CD57+ CTLs levels among CTL functional subsets

In line with current literature, AZA treatment significantly upregulated CTL levels at the 6th cycle (p=0.03). Non-responders to AZA had reduced levels of pretreatment PD1+ TCM CTLs (p=0.03) compared to responding patients but demonstrated a significant upregulation of the same subset at the 6th cycle of treatment (p=0.028), whereas PD1 expression on all CTL subsets remained unchanged in responders. Moreover, the levels of perforin+ CTLs, both on responders and non-responders, were not affected by AZA treatment.

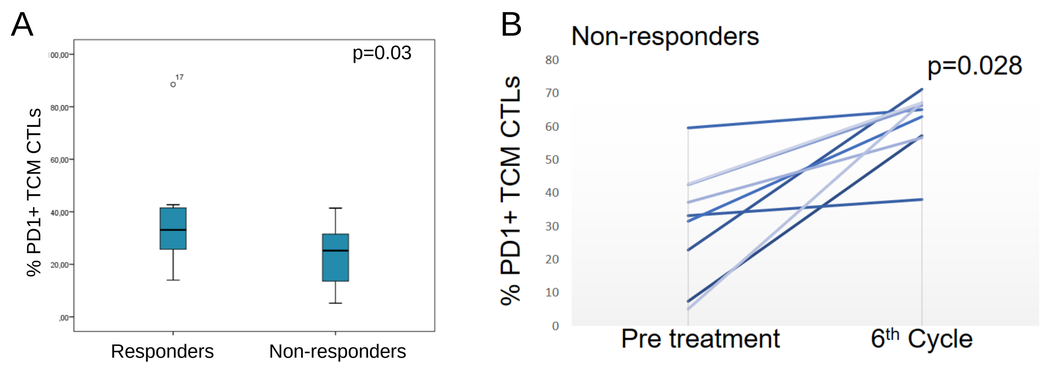

Figure 3. A. PD1+ TCM CTL levels in responders and non responders B. PD1+ TCM CTL levels in non responders, before AZA initiation and after the 6th cycle

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