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Immune correlates of metastatic melanoma patients treated with ipilimumab in combination with fotemustine in the phase II NIBIT-M1 study

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Background

Ipilimumab (IPI) in combination with fotemustine (FTM) has shown a promising clinical activity in metastatic melanoma (MM) patients (pts) enrolled in the NIBIT-M1 trial (Di Giacomo, et al., Lancet Oncology, 2012). This study investigated changes in immunological parameters in the course of treatment.

Material and methods

MM pts received an induction therapy with IPI 10 mg/kg every 3 weeks (Q3W) for four doses and FTM 100 mg/m2 weekly for 3 weeks. Peripheral blood lymphocytes (PBMC) and sera were collected at baseline, wk12, and wk24 to perform phenotypic and functional T cell assays, and to investigate humoral responses against a panel of tumor-associated antigens (TAAs) and soluble NKG2D ligands (sNKG2DL).

Results

Circulating central memory T (Tcm) cell populations, both CD4+ and CD8+, co-expressing CD45RO, CD27, CD28, CCR7, CD62L, were increased following treatment both at wk12 and wk24. Interestingly, T cells co-expressing CD4, BTLA and CD45RO were increased in pts with clinical benefit, while CD8+ Tcm co-expressing BTLA were augmented in pts with objective responses. Circulating T cells reactive against NY-ESO-1, MART-1, gp100 and TYRP-1, were found in 12/23 pts expressing at least one of the HLA-A1, A2, -A3 or A24 alleles with induction or augmentation of TAA reactivity in the course of treatment. Moreover, at least one sNKG2DL was found, though heterogeneously, in sera of 26/38 pts. Of note, in 10 pts, down-modulation of at least 2/4 investigated sNKG2DLs were detectable in relation with TAA-specific responses. Finally, at baseline, antibodies against NY-ESO-1, MAGE-A3, SSX-2, HMW-MAA, TYRP-1 and MSLN were found in sera of 9-15-8-7-7-6 of 40 investigated MM pts, respectively. Substantial changes were seen during therapy showing induced humoral responses against at least one investigated TAA in 10/40 pts at wk12 and/or wk24. In addition, up-regulation, equivalent to at least two-fold of the pre-existing antibody levels, against at least one TAA was detected in 5/40 pts at wk12 and/or wk24.

Conclusions

Our results, although preliminary, indicate that IPI in combination with FTM in MM pts induced changes in circulating T subpopulations and in their TAA-specific responses as well as in circulating antibodies to selected TAAs probably contributing to the observed clinical activity.

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