Background NY-ESO-1–specific T cells (letetresgene autoleucel [lete-cel]; GSK3377794) are autologous T cells transduced with a self-inactivating lentiviral vector to express an engineered NY-ESO-1–specific TCR that recognizes HLA-A*02–presented peptides derived from NY-ESO-1, a cancer/testis antigen expressed in 70%–80% of SS. NCT01343043 was a Phase I, open-label trial assessing safety, efficacy, and pharmacokinetics of lete-cel in patients with SS; activity was evaluated after different lymphodepletion conditioning regimens and in patients with differing levels of NY-ESO-1 expression. 

Methods Patients with unresectable, metastatic, or recurrent SS who were intolerant/nonresponsive to standard first-line chemotherapy enrolled in 4 cohorts based on NY-ESO-1 tumor expression were lymphodepleted and received lete-cel infusion (table 1). Primary endpoint was investigator-assessed overall response rate (ORR) per RECIST v1.1; secondary endpoints included duration of response (DoR), progression-free survival (PFS), overall survival (OS), and safety. Transduced cell persistence was measured by qPCR of transgene vector copies in DNA extracted from PBMCs. Study was not designed/powered to compare cohorts.

Results Overall, 50 patients enrolled; 45 received lete-cel infusion (modified intent-to-treat population). Demographics were similar between cohorts. Median time in study was 480/278/321/16.4 weeks; median PFS was 15.4/13.1/8.6/22.4 weeks (table 1). As of 27Jan2020, median OS for Cohorts 1/2/3 was 50% between cohorts, with 1–5 patients had SAEs [Grade ≥3 in 2 patients]; all AEs/SAEs resolved; Guillain-Barré syndrome in 2 patients (Grade 3 SAEs; resolved with sequelae); and multilineage cytopenias in 96% of patients (n=43; maximum Grade 5 in 1 patient, Grade 3/4 in others). Peak persistence of transduced cells was generally higher in responders vs non-responders (table 1); time to peak persistence was similar between these groups (median 8 days). No patients tested positive for replication-competent lentivirus.

Conclusions In patients with advanced SS who need effective treatment, lete-cel had a manageable safety profile; responses occurred in all cohorts, but patients with high NY-ESO-1 expression and more intensive lymphodepletion regimen received greatest benefit. 

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Background

The therapeutic efficacy of Dendritic cells (DC) vaccines remains low and there is an unmet need for more effective vaccine design to achieve durable clinical outcomes. Our study analyzed the transcriptomic and energetic metabolism profile of an adenoviral-based DC vaccine targeted against three commonly shared melanoma antigens: Tyrosinase, MART-1 and MAGE-A6 from 35 subjects enrolled in a Phase I study of autologous DC vaccines in late-stage melanoma. To further investigate the immune-metabolic features of monocyte-derived DC vaccines, we are employing a novel flow cytometry-based method, called SCENITH2 to integrate functional metabolic states with multiparametric DC immune phenotypes.

Methods

iDC were generated from HD and patient monocytes using GM-CSF+IL-4 for 5d. DC were matured using IFN?+LPS for additional 24 hrs. Tolerogenic DC (Tol DC) were generated using vitamin-D3 and dexamethasone. Seahorse™ was used to measure DC metabolic profile. Cytek/ Aurora spectral flow cytometry was used for multiparametric-phenotypic and metabolic analysis by SCENITH™.

Results

Melanoma patient mDC used for autologous vaccine generation showed significantly altered metabolic gene signatures associated with enhanced oxidative phosphorylation (OXPHOS) and lipid metabolism pathways as compared to HD mDC. Furthermore, increased enrichment for mitochondrial respiration genes involved in the TCA cycle, electron transport chain and fatty acid oxidation (FAO) correlated with inferior tumor antigen-specific T cell responses and clinical outcome in patients. Seahorse analyses confirmed that HD and good outcome patient DC demonstrated the highest maturation-induced reduction in maximal oxygen consumption rate/ OXPHOS and exogenous FAO. Interestingly, while the glycolytic rate of non-responding patient DC was the lowest, overall, we observe only a moderate increase in glycolytic capacity during DC maturation. SCENITH analysis showed that unlike monocytes, which are primarily glycolytic, differentiated mono-derived iDC and mDC utilize both glycolysis and mitochondrial respiration. Interestingly, under tolerogenic (Tol) differentiation conditions Tol iDC shift from glucose dependence into FAO and/or glutaminolysis while Tol mDC strongly depend on OXPHOS. Consistent with dependence on mitochondrial respiration, Tol mDC exhibit reduced HIF1a levels depend on OXPHOS. Consistent with dependence on mitochondrial respiration, Tol mDC exhibit reduced HIF1a levels depend on OXPHOS. Consistent with dependence on mitochondrial respiration, Tol mDC exhibit reduced HIF1a levels depend on mitochondrial respiration. Interestingly, under tolerogenic (Tol) differentiation conditions Tol iDC shift from glucose dependence into FAO and/or glutaminolysis while Tol mDC strongly depend on OXPHOS. Consistent with dependence on mitochondrial respiration, Tol mDC exhibit reduced HIF1a levels depend on mitochondrial respiration. Interestingly, under tolerogenic (Tol) differentiation conditions Tol iDC shift from glucose dependence into FAO and/or glutaminolysis while Tol mDC strongly depend on mitochondrial respiration. Interestingly, under tolerogenic (Tol) differentiation conditions Tol iDC shift from glucose dependence into FAO and/or glutaminolysis while Tol mDC strongly depend on mitochondrial respiration. Interestingly, under tolerogenic (Tol) differentiation conditions Tol iDC shift from glucose dependence into FAO and/or glutaminolysis while Tol mDC strongly depend on mitochondrial respiration.

Conclusion

We demonstrate that metabolic profile of DCs is tightly associated to the immuno-stimulatory potential of DC vaccines from cancer patients. Using SCENITH, we linked phenotypic and functional metabolic changes associated to immune signatures that correspond to healthy and immuno-suppressed DC differentiation.

Ethics Approval

The clinical trial reported was fully approved by the Univ. Pittsburgh PRC and IRB (PRO12010416, #09–021) and had FDA IND #15044 and NCT01622933.

REFERENCES