Pathology & Oncology Research (2020) 26:1355–1356
https://doi.org/10.1007/s12253-019-00653-w

LETTER TO THE EDITOR

Immune Checkpoint Inhibitors in Small Cell Lung Cancer: Is It Also a Matter of Helios– Cells?

Raffaella Mormile[1]

Received: 27 February 2019 / Accepted: 24 March 2019 / Published online: 29 March 2019

Small cell lung cancer (SCLC) represents an aggressive condition with no therapeutic options inducing long-lasting responses [1]. Patients who have undergone two or more previous lines of therapy for SCLC are often symptomatic from progression of cancer, side effects of previous therapy, and comorbidities [1]. Patients affected by SCLC who have progressed despite multiple lines of management have few therapeutic possibilities in the third line and beyond [1]. Recently, early reports from studies with immune checkpoint inhibitors have demonstrated encouraging results with the potential for long term disease control in a subset of SCLC patients [2]. Blockade of programmed death receptor-1 (PD-1)/programmed death ligand 1 (PD-L1) axis has been proposed as a promising treatment for metastatic SCLC beyond the frontline [2]. PD-L1 expression status of tumor cells is usually utilized to select patients who might be more likely to benefit from immune checkpoint inhibitors [2]. SCLC tumor cells have been suggested to modulate responses of CD4(+) T cells from healthy donors [3]. The CD4+ T lymphocytes have a critical role in anti-tumor immune responses [3]. The CD4+ T cell subset include regulatory T (Treg) cells [4]. There are two broad Treg subsets that show the transcription factor forkhead box protein P3(FOXP3) [3]. FOXP3-expressing T regulatory cells (Tregs) are divided in naturally occurring Tregs (nTregs) and induced Tregs (iTregs) that differentiate in peripheral tissues upon exposure to Ag in a tolerogenic environment [4]. Helios, an Ikaros family transcription factor, has been linked to transcription factor FOXP3 expression [4]. Expression of Helios, has been proposed to specifically identify nTregs, allowing specific tracking of Tregs from different origins in health and disease [4]. It has been reported that Helios+ and Helios– cells coexist within the natural FOXP3 + T Regulatory Cell Subset in Humans [4]. Helios-nTreg clones have been found to show a suppressive capacity, as well as expression of FOXP3 and cell surface proteins similar to Helios+ nTreg clones, with the notable exception of higher production of IFNɣ [4]. Some SCLC tumor cell lines have been connected with de novo differentiation of functional CD4(+)CD25(+)FOXP3(+)CD127$^{(lo)}$Helios(−) regulatory T (Treg) cells in healthy blood lymphocytes [3]. Increased evidence has suggested that IFN-γ can act to promote tumor progression [5]. It has been observed that IFN-ɣ can promote tumor cells to evade immune surveillance [5]. It has been proved that that lung cancer cells cultured with supernatant of tumor-associated macrophages induce the expression of PD-L1 by the secretion of IFN-γ [5]. PD-L1 induced by IFN-γ from tumor-associated macrophages has been linked to progression of lung cancer [5]. Taken together, I hypothesize that SCLC cells may lead to increased expression of PD-L1 through up-regulation of IFN-γ by increasing differentiation of Helios- cells. For that reason, I suppose that the potential of an interaction between PD-L1 and IFN-ɣ axis via Helios- cells in SCLC progression may represent a warranted reason for using PD-L1/PD-1 inhibitors in SCLC management. Further research is needed for selecting appropriate patient subpopulations for clinical trials.

Compliance with Ethical Standards

Conflict of Interest The author declares no potential conflicts of interest.

References

1. Ready N, Farago AF, de Braud F, Atmaca A, Hellmann MD, Schneider JG, Spigel DR, Moreno V, Chau I, Hann CL, Eder JP, Steele NL, Pieters A, Fairchild J, Antonia SJ (2018) Third-line nivolumab monotherapy in recurrent sclc: check mate 032. J Thorac Oncol. 2018 Oct 10. pii: S1556–0864(18)33181–2.0998079
2. Schmid S, Früh M (2018) Immune checkpoint inhibitors and small cell lung cancer: what's new? Thorac Dis 2018 May;10(Suppl 13): S1503–S1508

✉ Raffaella Mormile
raffaellamormile@alice.it

[1] Division of Pediatrics and Neonatology, Moscati Hospital, Via A. Gramsci, 81031 Aversa, Italy

3. Wang W, Hodkinson P, McLaren F, MacKinnon A, Wallace W, Howie S, Sethi T (2012 Sep 15) Small cell lung cancer tumour cells induce regulatory T lymphocytes, and patient survival correlates negatively with FOXP3+ cells in tumour infiltrate. Int J Cancer 131(6):E928–E937
4. Himmel ME1, MacDonald KG, Garcia RV, Steiner TS, Levings MK. Helios+ and Helios- cells coexist within the natural FOXP3+ T regulatory cell subset in humans. J Immunol 2013 Mar 1;190(5):2001–2008
5. Zhang X, Zeng Y, Qu Q, Zhu J, Liu Z, Ning W, Zeng H, Zhang N, Du W, Chen C, Huang JA (2017 Dec) PD-L1 induced by IFN-γ from tumor-associated macrophages via the JAK/STAT3 and PI3K/AKT signaling pathways promoted progression of lung cancer. Int J Clin Oncol 22(6):1026–1033