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#227P Sexual Dimorphism in immune profile of early and advanced NSCLC

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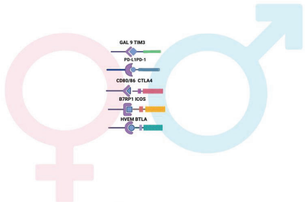
BACKGROUND

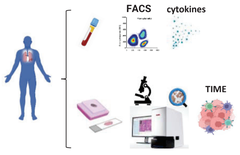
We determined whether sex-associated tissue and blood immune background characterizes surgically resected NSCLC and advanced patients undergoing immunotherapy (IO), potentially affecting clinical outcome.

METHODS

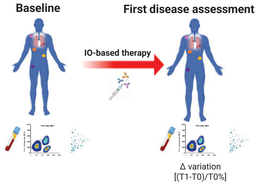
Peripheral blood, collected at surgery from 120 stage I-III, and at baseline and first disease assessment (T1) from 152 (chemo)-IO treated NSCLC, was subjected to FACS analysis of multiple cellular immunophenotypic and functional properties and to multiplex ELISA assay to measure serum cytokines. Tumor Immune Microenvironment (TIME) was assessed by IHC on surgical samples. These parameters were statistically correlated with clinical characteristics.



Surgical cohort



Metastatic cohort



Clinicopathological Characteristics

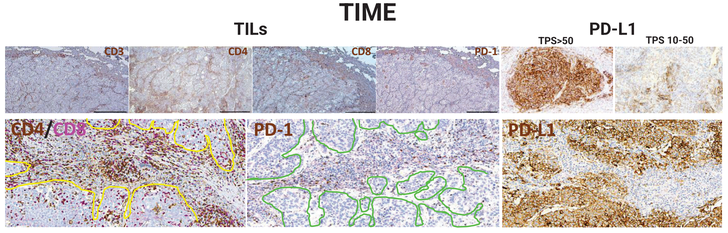
		Male N 63	Female N 57
Age, years, median (range)		72 (46-82)	70 (47-82)
		n (%)	
WHO Histology	ADC	44 (69.8)	51 (89.5)
	SCC	18 (28.5)	6 (10.5)
	Combined (ADC-SCC)	1 (1.7)	0
Smoking status	Never Smokers	2 (3.2)	14 (24.6)
	Former / Current Smokers	61 (96.8)	43 (75.4)
ECOG PS	0-1	39 (61.9)	43 (75.4)
	2	24 (38.1)	14 (24.6)
Recurrence	No	51 (80.9)	47 (82.4)
	Yes	12 (19.1)	10 (17.6)
Resection status	R0	57 (90.5)	56 (98.2)
	R1	6 (9.5)	1 (1.8)
pTNM Stage	I (IA, IB)	39 (61.9)	32 (56.1)
	II (IIA, IIB)	15 (23.8)	15 (26.3)
	III (IIIA-IIIB)	9 (14.2)	10 (17.5)
PD-L1, TPS score	>50%	9 (15.8)	7 (13.7)
	10-50%	6 (10.5)	5 (9.8)
	1-10%	27 (47.3)	17 (33.3)
	<1%	13 (22.8)	22 (43.1)
Comorbidity	No	19 (30.1)	34 (59.6)
	Yes	44 (69.9)	23 (40.3)

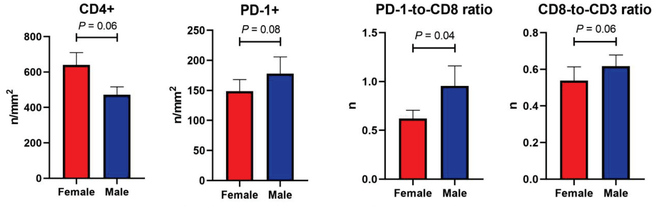
		Male N 101	Female N 51
Age, years, median (range)		69.4 (41-88)	67.5 (54-82)
		n (%)	
WHO Histology	ADC	77 (76.2)	39 (76.4)
	SCC	17 (22.1)	6 (11.7)
	NSCLC NOS	7 (6.9)	6 (11.8)
Smoking status	Smokers	37 (36.6)	21 (41.2)
	Ex-Smokers	58 (57.4)	19 (37.2)
	Non Smokers	5 (4.9)	9 (17.6)
ECOG PS	0-1	88 (87.1)	47 (92.2)
	2	13 (12.9)	4 (7.8)
Number of metastatic sites	< 3	38 (37.6)	23 (45.1)
	≥ 3	63 (62.4)	28 (54.9)
Metastatic Involvement	Bone	40 (39.6)	16 (31.3)
	Brain	27 (26.7)	12 (23.5)
	Liver	12 (11.8)	6 (11.8)
	Lung	72 (71.2)	38 (74.5)
	Lymph nodes	86 (85.1)	43 (84.3)
	Adrenal gland	20 (19.8)	10 (19.6)
	Pleura	15 (14.8)	6 (11.7)
Treatment type	Immunotherapy	40 (39.6)	21 (41.2)
	Chemo-immunotherapy	61 (60.4)	30 (58.8)
PD-L1, TPS score	> 50%	23 (22.8)	15 (29.4)
	10-50%	11 (10.9)	5 (9.8)
	1-10%	38 (37.6)	17 (33.3)
	< 1%	23 (22.8)	13 (25.4)

WHO: world health organization; ADC: adenocarcinoma; SCC: squamous cell carcinoma; ECOG PS: Easter Cooperative Oncology Group Performance Status; TPS: tumor proportion score.

SURGICAL COHORT

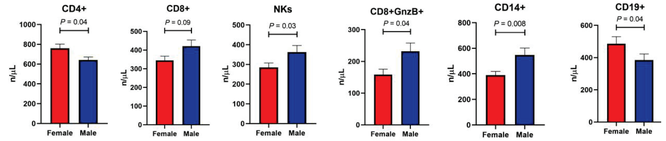
TIME



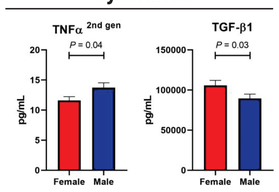


Tumor Immune Microenvironment (TIME). Top panel: serial sections from a surgically resected NSCLC to illustrate on the same microscopic field the detection of CD3, CD4, CD8 and PD-1 Tumor Infiltrating Lymphocytes (TILs) by immunoperoxidase (brown). Representative images of the different extent of PD-L1 expression by tumor proportion score (TPS) are shown on the right. Bottom panel: serial sections from a NSCLC sample sequentially illustrating the simultaneous detection of CD4+ (brown) and CD8+ (purple) by double immunostaining, and PD-1+ (brown) TILs as the extensive PD-L1 expression by tumor cells on the same tissue area. Manually drown yellow and green lines inscribe neoplastic nodules bulging into the interstitial space to underline the two areas on which TILs were separately recorded. Bar graphs to document the quantification of TILs number and ratio within the TIME from surgically resected female and male NSCLC samples.

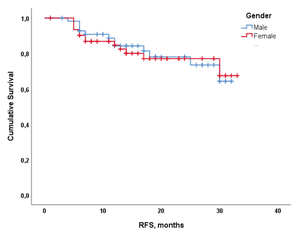
Blood immune-inflammatory profiling



Cytokines



Survival Outcome



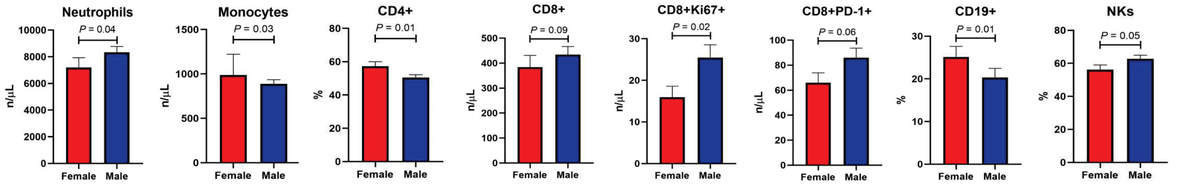
Top: Bar graphs illustrating the differential extent of baseline circulating T (CD4, CD8), NKs and CD19+ B cells, and CD14+ monocytes in female and male NSCLC patients undergoing surgical resection. GnzB: granzyme B. Bottom: bar graphs documenting the quantification of TNFα and TGF-β1 plasma levels in the same population. The impact of gender on relapse free survival (RFS) in the surgical cohort of NSCLC is shown by the Kaplan Meier curve.

RESULTS

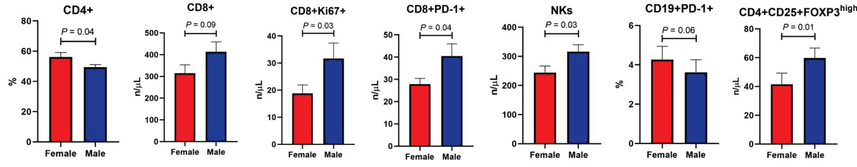
METASTATIC COHORT

Blood immunophenotypic profiling of IO-treated male and female NSCLC patients

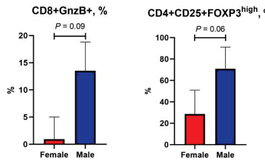
Baseline (T0)



First disease assessment (T1)

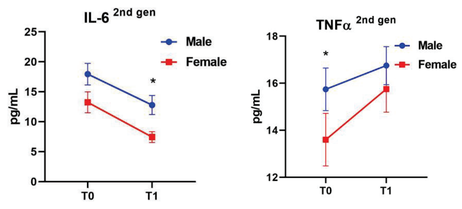


Delta (Δ) variation



Bar graphs illustrating the values of blood neutrophils and different subpopulations of immune cells at baseline (T0), first disease assessment (T1) and their delta (Δ) variation in female and male patients undergoing IO treatment. GnzB: granzyme B. P values are referred to Mann Whitney test.

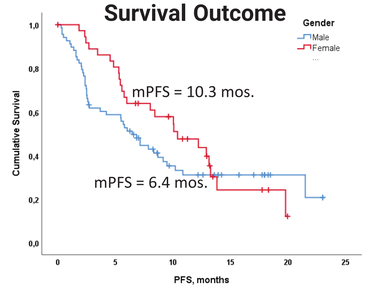
Cytokines



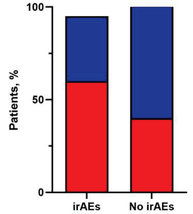
Line graphs illustrating the different modulation of interleukin-6 (IL-6) and Tumor Necrosis Factor α (TNFα) plasma levels as measured at baseline (T0) and first disease assessment (T1) in female and male patients undergoing IO treatment.
* indicates P values <0.05 based on Wilkoxon rank test (female vs male subsets) at T0 and T1, respectively.

Impact of Sex on Clinical Outcome

Survival Outcome



irAEs onset



Left: Kaplan Meier curves showing the effect of gender on progression free survival (PFS) in the population of advanced NSCLC patients subjected to IO-based therapy. Right: stacked bar charts illustrating the distribution of male and female patients according to the presence or absence of immune related adverse events (irAEs).

CONCLUSION

The immunity of early and advanced NSCLC patients is trained by gender which might contribute to the heterogeneity of tumor-host interaction and its clinical impact.

The present study is part of a 5-years project funded by Associazione Italiana di Ricerca sul Cancro (AIRC) gathering radiologists, pathologists, molecular biologists and oncologists to test multiomic approaches able to assess the response to immunotherapy in NSCLC. I have nothing to disclose.

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