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Abstract category: Clinical hemato-oncology

Gender-specific effects of tumour infiltrating clonal haematopoiesis on overall survival in NSCLC

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Background

Clonal hematopoiesis (CH), a common age-associated phenomenon, has been shown to be associated with adverse cancer outcomes, including progression-free and overall survival in non–small-cell lung cancer (NSCLC). Emerging evidence suggests that tumor-infiltrating CH (TI-CH) may affect the anti-tumor immune response; however, the clinical relevance, particularly in the context of first or second line-line ICI therapy remains to be confirmed. To our knowledge, gender-specific differences in the adverse effect of TI-CH have not been reported so far.

Methods

In this retrospective analysis we analyzed 114 patients with all stage adeno-NSCLC diagnosed and treated at our institution, including 35 patients with confirmed CH mutations. TI-CH was detected by searching for subclonal pathogenic mutations in the genes *TET2*, *DNMT3A*, *ASXL1*, *JAK2*, *SF3B1* and *U2AF1* associated with CH in the mutational profile of tumour samples as obtained by the FoundationOne testing. We used propensity score matching to balance known confounders between the groups. Kaplan-Meier analyses were performed to evaluate the impact of CH status on progression-free (PFS) and overall survival (OS) across different therapies (TKI, ICI and Chemotherapy) and between male and female patients and Cox Proportional Hazards models were used to calculate hazard ratios.

Results

In our cohort, patients with TI-CH had a significantly increased risk of all-cause death (HR=2.26, 95% CI 1.25-4.07, p=0.007) and decreased progression free survival after first-line therapy (HR=2.11, 95% CI 1.26-3.50, p=0.004), confirming findings of previous studies. Interestingly, we observed a gender-based difference in the influence of TI-CH on outcomes in chemotherapy including regiments: While males showed no significant difference in PFS with TI-CH (HR=1.08, 95%CI=0.60-1.95, p=0.78) females showed a severely decreased PFS with TI-CH (HR=4.12, 95% CI 1.55-10.94, p=0.004).

Conclusion

Our findings highlight the role of TI-CH as an important risk factor on outcomes in NSCLC and to our knowledge for the first time suggest gender-specific effects of TI-CH. Although we cannot exclude that our results are spurious given the small single-center cohort, gender-differences in the adverse effect of TI-CH in the context of treatment might explain our findings, and further studies including larger cohorts are necessary to confirm our results.

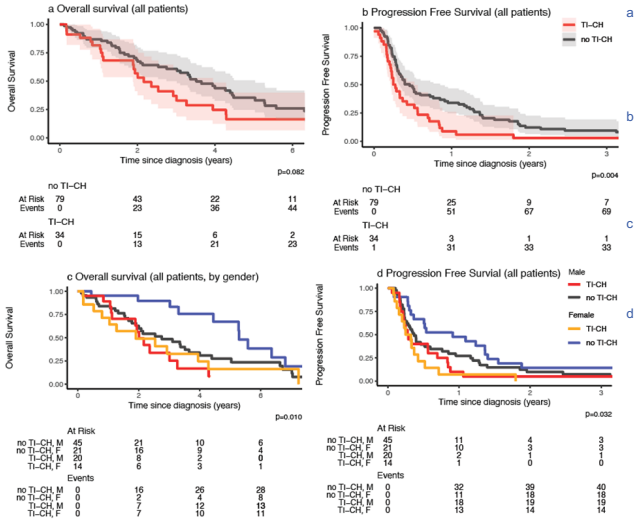
Baseline characteristics

Characteristic	N	no TI-CH N = 79[1]	TI-CH N = 35[1]	p-value[2]
Sex	114			0.7
female		31 (39%)	15 (43%)	
male		48 (61%)	20 (57%)	
Age at diagnosis	114	65 (59 - 71)	69 (65 – 74)	**0.026***
ECOG at diagnosis	111			**0.015***
1		56 (73%)	18 (53%)	
2		19 (25%)	10 (29%)	
3, 4		2 (2%)	6 (18%)	
unknown		2	1	
CPR at diagnosis mg/L	104	7 (2 – 22)	8 (2 – 38)	0.2
unknown		5	5	
Firstline setting	113			**0.032***
curative		25 (32%)	18 (53%)	
palliative		54 (68%)	16 (47%)	
unknown		0	1	
Stage (UICC)	113			0.5
1		6 (8%)	5 (15%)	
2		7 (9%)	3 (6%)	
3		16 (19%)	10 (30%)	
4		50 (63%)	16 (48%)	
unknown		0	1	

[1]n (%); Median (Q1, Q3), [2]Pearson's Chi-squared test; Wilcoxon rank sum test; Fisher's exact test

Cohort Description
Patients were stratified by presence or absence of TI-CH. As expected, patients with TI-CH were significantly older and had a worse ECOG performance score at diagnosis; a higher proportion of patients with TI-CH were in the curative therapeutic setting.

Kaplan-Meier Analysis of the entire cohort



a Overall survival analysis of all patients included in this study. The group with TI-CH is shown in red, while the group without TI-CH is shown in gray.

b Progression Free Survival after diagnosis of all patients included in this study. The group with TI-CH is shown in red, while the group without TI-CH is shown in gray.

c Overall survival analysis of all patients stratified by gender and the presence of TI-CH. The colour legend is shown in panel d.

d Progression Free Survival analysis of all patients after diagnosis stratified by gender and the presence of TI-CH.

Analysis of PFS for all therapy lines in the palliative setting

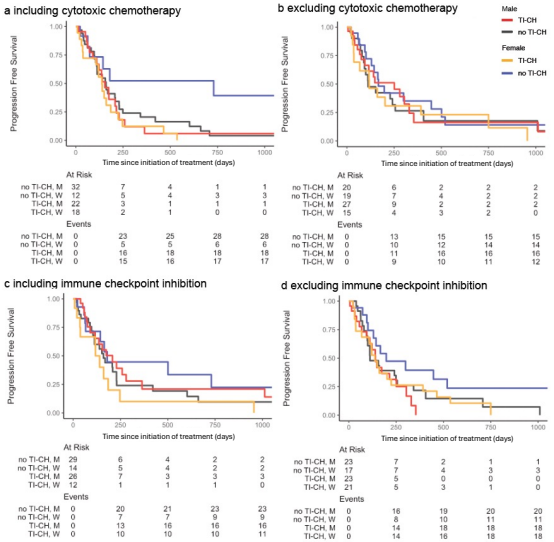
PFS was calculated for all therapy lines the palliative setting and propensity-score matching of therapy lines was used to obtain comparable cohorts. PFS was determined on corresponding clinical and radiological treatment responses, as well as the recorded dates of death or last follow-up.

a PFS of therapy lines including cytotoxic chemotherapy shows similar outcomes for males with and without TI-CH while PFS deteriorates in female patients with TI-CH compared to female patients without TI-CH.

b PFS of therapy lines without cytotoxic chemotherapy does not show obvious differences between the groups.

c PFS of therapy lines with immune checkpoint inhibition (ICI) shows no obvious differences between groups, although females without TI-CH do slightly better than females with TI-CH.

d PFS of therapy lines without ICI showed no obvious differences between the groups.



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