SOHO ANNUAL MEETING 2024

THE ROLE OF NK-CELLS IN RESISTANCE CHRONIC MYELOID LEUKEMIA PATIENTS TO TYROSINE KINASE INHIBITORS

L. O. Khordzhasov[1], T. V. Chitanava[1], R. A. Vlasik[1], A. Ataman[1], N. S. Luchkina[1], A. Yu. Aronov[1], Yu. D. Matvienko[1], N. T. Siordiya[1], O. V. Kulemina[1], N. S. Lazorko[1], E. I. Sbityakova[1], N. A. Shnalieva[1], E. N. Tochenaya[1], Yu. A. Alekseeva[1], P. A. Butylin[1], S. V. Smirnov[1], E. G. Lomaia[1]

[1] Personalized Medicine Centre, Almazov National Medical Research Centre, 2 Akkuratova Str., Saint Petersburg, Russian Federation, 197341

ALMAZOV National Medical Research Centre

INTRODUCTION

The mechanisms of resistance to tyrosine kinase inhibitors (TKI) in chronic myeloid leukemia (CML) aren't fully understood. In the present study, we analyze whether NK cells might have play a role in the response to TKI.

AIM

The goal of this prospective research is to evaluate the role of NK-cells and KIR haplotypes in the development of resistance to TKI therapy in CML CP patients.

METHOD

- Overall, 40 patients with CML in first chronic phase (CP) resistant (non-responders) or with optimal response (responders) to two prior TKIs and 20 healthy donors were enrolled in our study. The median age was in patient's and in healthy donors 53 (26–70) years and 32 (23–59) years, respectively.
- As a third line TKI patients received bosutinib n=5 (12,5%), dasatinib n=13 (32,5%), and nilotinib n=22 (55%).
- Patients received third line TKI at least 1 year with (n=20) or without (n=20) molecular response 2 (equal BCR::ABL <1%).
- Expressions of NK, TNK cells, activating and inhibiting receptors on NK cells were evaluated by flow cytometry, The KIR receptor's haplotype was defined by PCR and protein electrophoresis.

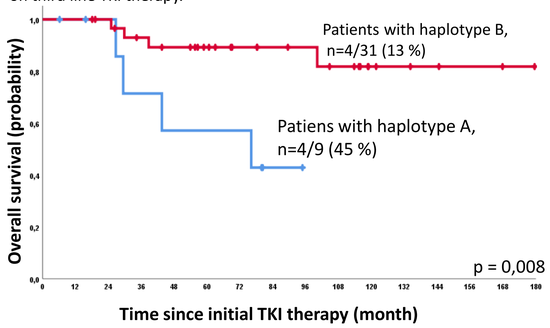
REFERENCES

1. Bayigga L. et al. High CD56++ CD16-natural killer (NK) cells among suboptimal immune responders after four years of suppressive antiretroviral therapy in an African adult HIV treatment cohort //BMC immunology. – 2014. – Т. 15. – С. 1-8.
2. Frutoso M., Mair F., Prlic M. OMIP-070: NKp46-based 27-color phenotyping to define natural killer cells isolated from human tumor tissues //Cytometry Part A. – 2020. – Т. 97. – №. 10. – С. 1052-1056.
3. Chitanava T. et al, The prediction factors of efficiency second generation TKI on third-line therapy CML CF. – 2024. dissertacia_chitanava.pdf (bloodscience.ru)

RESULTS

- ✓ Median expression of level of NK and TNK cells was 9% and 5 % vs 11% and 5% vs 7% and 5%, respectively, in the healthy donors, responders and non-responders (p>0,05).
- ✓ In these groups median fraction of activating NKp46 (CD335) and inhibiting KIR (CD158 e1/e2) receptors of NK-cells was 0.5% and 0,5% vs 0.7% and 0.2% vs 0.5% and 0.3%, respectively (p>0,05).
- ✓ Comparisons of KIR genes' expression, the quantity of activating and inhibiting KIR, KIR genotypes in responders, non-responders, and healthy donor groups are presented in Tab. 1. Much more patients in responder group expressed activating KIR2DS4 and KIR3DS1 than in non-responders or healthy group. Meanwhile more CML patients in both groups expressed KIR3DL2 receptor than donors.
- ✓ In all 3 groups haplotype Bx of KIR was predominantly detected. Estimated MR2 by 12 months was 11% and 43% of patients with A and Bx haplotype, respectively (0,096).
- ✓ 4-year overall survival was 59% vs 87% in cases with haplotype A vs Bx (p=0,008) (Pic. 1).

Pic. 1. OS probability for CML patients with haplotype A and haplotype B on third line TKI therapy.



Tabl. 1. Comparisons of KIR genes' expression, the quantity of activating and inhibiting KIR, KIR genotypes in responders, non-responders, and healthy donor groups .

KIR receptors expression		Healthy donors, n=20, n (%)	Responders, n=20, n (%)	Non-responders, n=20, n (%)	p
Expression of activating KIR	KIR2DS1	6 (30 %)	8 (40 %)	9 (45 %)	0,61
	KIR2DS2	10 (20 %)	13 (65 %)	8 (40 %)	0,28
	KIR2DS3	3 (15 %)	6 (30 %)	6 (30 %)	0,45
	KIR2DS4	13 (65 %)	19 (95 %)	11 (55 %)	0,02
	KIR2DS5	1 (5 %)	5 (25 %)	4 (20 %)	0,21
	KIR3DS1	2 (10 %)	9 (45 %)	6 (30 %)	0,04
Expression of inhibiting KIR	KIR2DL1	20 (100 %)	19 (95 %)	18 (90 %)	0,35
	KIR2DL2	10 (50 %)	13 (65 %)	9 (45 %)	0,42
	KIR2DL3	19 (95 %)	16 (80 %)	16 (80 %)	0.31
	KIR2DL4	18 (90 %)	20 (100 %)	19 (95 %)	0,58
	KIR2DL5	8 (40 %)	9 (45 %)	5 (25 %)	0,39
	KIR3DL1	6 (30 %)	11 (55 %)	12 (60 %)	0,13
	KIR3DL2	9 (45 %)	19 (95 %)	17 (85 %)	0,01
	KIR3DL3	20 (100 %)	18 (90 %)	19 (95 %)	0,35
Quantity of activating KIR per patient	0	2 (10 %)	1 (5 %)	1 (5 %)	0,76
	1	8 (40 %)	3 (15 %)	7 (35 %)	0,19
	>2	10 (50 %)	16 (80 %)	12 (60 %)	0,14
Quantity of inhibiting KIR per patient	6	17 (85 %)	10 (50 %)	3 (65 %)	0,01
	7	2 (10 %)	8 (40 %)	5 (25 %)	0,09
	8	1 (5 %)	2 (10 %)	2 (10 %)	0,83
The type of KIR Haplotypes	AA	4 (20 %)	3 (15 %)	6 (30 %)	0,50
	Bx	16 (80 %)	17 (85 %)	14 (70 %)	1,00

CONCLUSIONS

In our cohort of patients (responders vs non-responders) vs healthy donors no statistically differences were observed in the level of expression of NK, TNK cells and prevalence of KIR haplotypes. Patients with haplotype B vs A had slightly higher MR2 and had significantly better overall survival. More responders expressed some type of activating KIR receptors. In our cohort of heavily pretreated CML patients there were none to moderate differences in the level of NK-cells, it receptors or haplotypes versus healthy donors or even depending on the response to TKI therapy.

ACKNOWLEDGEMENTS

The work was financially supported by the Ministry of Science and Higher Education of the Russian Federation (Agreement No. 075-15-2022-301)

CONTACT INFORMATION

L. Khordzhasov 631643@mail.ru
E.Lomaia: lomelza@gmail.com
T.Chitanava: chitanava.tamara@yandex.ru