Tocilizumab administration in cytokine release syndrome is associated with hypofibrinogenemia after chimeric antigen receptor T-cell therapy for hematologic malignancies

Markus Perl,[1] Konstantin Herfeld,[1] Dennis C. Harrer,[1] Matthias Höpting,[1] Marina Schweiger,[1] Ulrich Sterz,[1] Leonard Knödler,[1] Susanne Heimerl,[2] Leo Hansmann,[1] Wolfgang Herr,[1] Hendrik Poeck,[1] Daniel Wolff,[1] Matthias Edinger,[1,3] Christina Hart[1#] and Matthias A. Fante[1#]

[1]Department of Internal Medicine III, University Medical Center Regensburg; [2]Department of Clinical Chemistry, University Medical Center Regensburg and [3]Leibniz Institute for Immunotherapy (LIT), Regensburg, Germany

[#]CH and MAF contributed equally as senior authors.

Correspondence: M.A. Fante
matthias.fante@ukr.de

Received: October 31, 2023.
Accepted: March 22, 2024.
Early view: March 28, 2024.

https://doi.org/10.3324/haematol.2023.284564

Supplemental Table S1. Devices and methods used for determination of presented parameters

parameter	normal range	company	analyzer	method
alanine transaminase (ALT)	0 - 35 U/l (female) / 0 – 50 U/l (male)	Roche	Cobas pro C-503	Photometry
albumin	35 – 52 g/l	Roche	Cobas pro C-503	Photometry
cholinesterase (CHE)	5320 – 12920 U/l	Roche	Cobas pro C-503	Photometry
D-dimers	< 0.5 mg/l	Siemens	BCS-XP	Immunoturbidimetry
fibrinogen	210 – 400 mg/dl	Siemens	BCS-XP	Coagulometry
gamma-glutamyltransferase (gGT)	< 40 U/l (female) / < 60 U/l (male)	Roche	Cobas pro C-503	Photometry
international normalized ratio (INR)	0.85 – 1.15	Siemens	BCS-XP	Coagulometry
partial thromboplastin time (PTT)	25.9 – 36.6 sec.	Siemens	BCS-XP	Coagulometry
platelets	182 – 369 G/l (female) / 163 – 337 G/l (male)	Sysmex	XN10 /XN20	Fluorescence flow cytometry, electrical impedance

Supplemental Table S2: Patient characteristics categorized by CRS grades and utilization of tocilizumab

	CRS grade 0	**CRS grade 1**		**CRS grade 2**		**CRS grade 3**	**CRS grade 4**
	w/o toci (n=3)	*w/o toci (n=7)*	*with toci (n=6)*	*w/o toci (n=2)*	*with toci (n=18)*	*with toci (n=3)*	*with toci (n=2)*
median age, years (range)	67 (49-73)	71 (54-77)	62 (49-71)	57.5 (47-68)	72.5 (38-78)	69.0 (64-69)	73 (63-83)
female sex, n (%)	1 (33)	4 (57)	3 (50)	1 (50)	12 (67)	1 (33)	0 (0)
disease, n (%)							
high-grade B-NHL	2 (67)	5 (71)	3 (50)	2 (100)	16 (89)	1 (33)	1 (50)
multiple myeloma	0 (0)	2 (29)	2 (33)	0 (0)	1 (6)	0 (0)	0 (0)
follicular lymphoma	1 (33)	0 (0)	1 (17)	0 (0)	0 (0)	1 (33)	0 (0)
mantle cell lymphoma	0 (0)	0 (0)	0 (0)	0 (0)	1 (6)	0 (0)	1 (50)
acute leukemia	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (33)	0 (0)
CAR-T cell product, n (%)							
Tisagenlecleucel	2 (67)	5 (71)	3 (50)	0 (0)	8 (44)	0 (0)	0 (0)
Axicabtagene ciloleucel	1 (33)	0 (0)	1 (17)	2(100)	7 (39)	2 (67)	1 (50)
Idecabtagene vicleucel	0 (0)	2 (29)	2 (33)	0 (0)	1 (6)	0 (0)	0 (0)
Brexucabtagene autoleucel	0 (0)	0 (0)	0 (0)	0 (0)	1 (6)	1 (33)	1 (50)
experimental CAR	0 (0)	0 (0)	0 (0)	0 (0)	1 (6)	0 (0)	0 (0)
hypofibrinogenemia, n (%)							
de novo hypofibrinogenemia	0 (0)	0 (0)	5 (83)	0 (0)	18 (100)	3 (100)	1 (50)
median fibrinogen nadir, mg/dl (range)	256 (190-260)	293 (218-401)	146 (120-230)	377 (273-481)	112 (40-205)	74 (63-86)	145 (65-259)
fibrinogen replacement	0 (0)	0 (0)	0 (0)	0 (0)	5 (28)	2 (67)	1 (50)
other coagulation factor replacement	0 (0)	0 (0)	1 (17)	0 (0)	6 (33)	1 (33)	2 (100)
corticosteroid use, n (%)	0 (0)	1 (14)	2 (33)	0 (0)	6 (33)	3 (100)	2 (100)

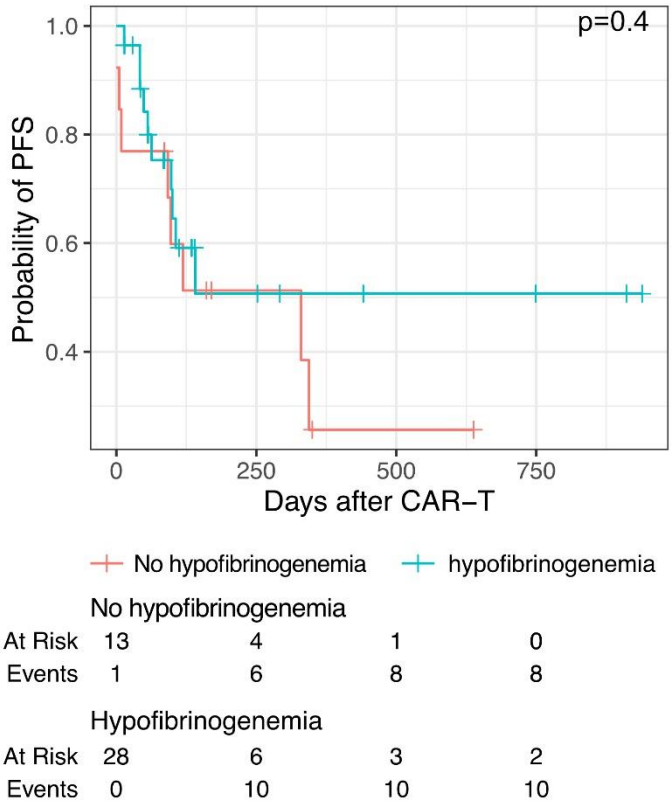
Abbreviations: CRS – cytokine release syndrome, w/o – without, toci – tocilizumab, n – number of patients, CAR – chimeric antigen receptor

Supplemental Table S3: Multivariate regression analysis for hypofibrinogenemia after CAR-T cell therapy

	Odds ratio	*p value*
Tocilizumab use	**486**	**<0.001**
Bulky disease	2.04	0.73
Charlson Comorbidity Index [per point]*	1.38	0.66
CD28 costimulatory domain	1.17	0.92
Maximum D-dimers [per 1 mg/l]	0.83	0.16
Age [per 5 years]	0.81	0.53
Minimum cholinesterase [per 500 U/l]	0.71	0.38
Full-dose lymphodepletion	0.32	0.75
Number of patients	41	
Pseudo R2	0.80	

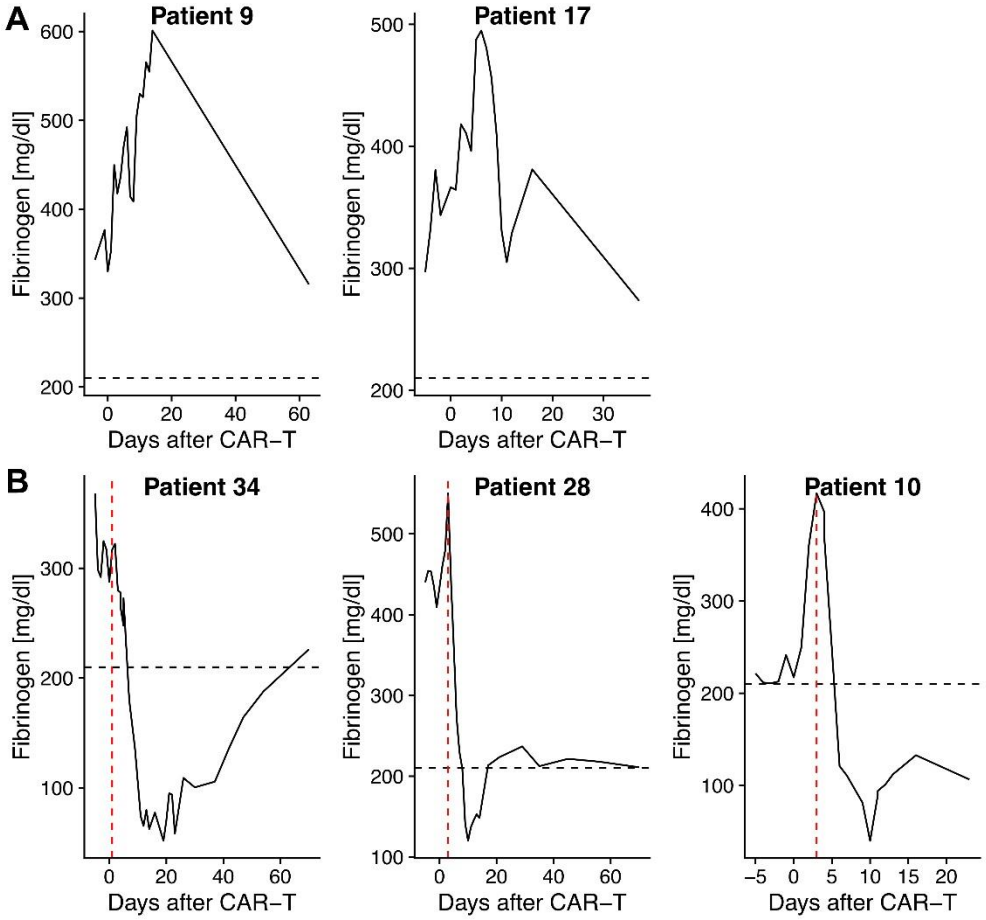
**lymphoma/leukemia and age excluded from Charlson Comorbidity Index*

Supplemental Figure S1



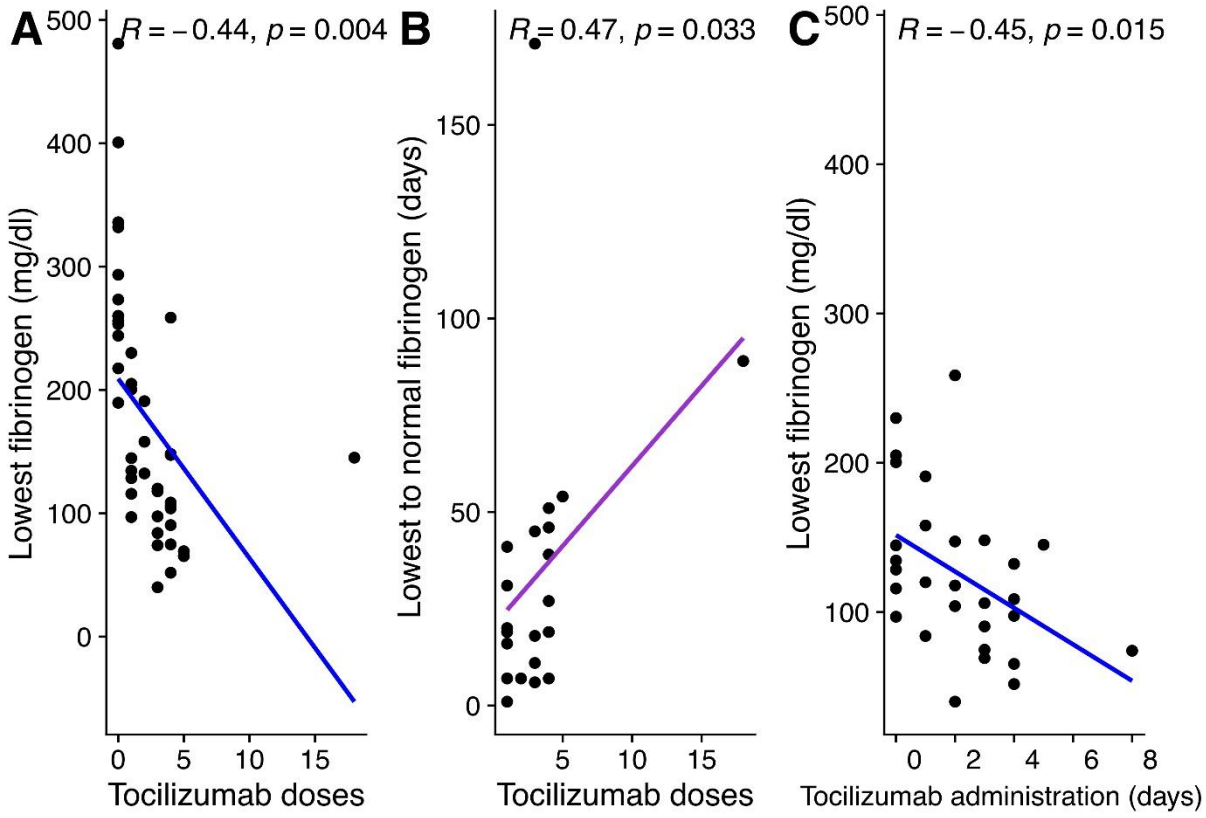
Supplemental Figure S1: Progression-free survival (PFS) in patients with (blue) and without (red) hypofibrinogenemia. Groups are compared by log-rank test.

Supplemental Figure S2



Supplemental Figure S2: Fibrinogen values of individual patients with and without tocilizumab administration. (A) Patients developing CRS without tocilizumab treatment experience an increase in fibrinogen levels, **(B)** whereas tocilizumab administration results in a rapid decline in fibrinogen levels. Dashed horizontal lines (black) represent the lower limit of normal of fibrinogen levels, dashed vertical lines (red) indicate the day of first tocilizumab administration.

Supplemental Figure S3



Supplemental Figure S3: (A, B) Numbers of tocilizumab doses correlate with the extend and duration of hypofibrinogenemia. **(C)** Duration of tocilizumab administration inversely correlates with fibrinogen levels.