Abstract: P1536

Title: REAL-WORLD EXPERIENCE OF IMMUNOCHEMOTHERAPY IN COLD AGGLUTININ DISEASE AND COLD AGGLUTININ SYNDROME

Abstract Type: Poster Presentation

Topic: Enzymopathies, membranopathies and other anemias

Background:

Cold auto-immune hemolytic anemia (cAIHA) is caused by IgM autoreactive antibodies against red blood cells, that lead to complement-mediated hemolysis and sometimes acrocyanosis. cAIHA is classified into Cold Agglutinin Disease (CAD) and Cold Agglutinin Syndrome (CAS). In CAD, a low-grade B-cell lymphoproliferative disease (LPD) or paraproteinemia are typically present, without extramedullary involvement. CAS can be secondary to overt lymphoid malignancies, including Waldenström macroglobulinemia (WM) and chronic lymphocytic leukemia (CLL). While Rituximab (R) monotherapy leads to only partial and short-lived responses in CAD, one prospective study showed that R-bendamustine yields improved and more durable responses, albeit with more toxicities. Data on the effect of other immunochemotherapy (ICT) regimens, such as R-cyclophosphamide-based therapy, and response in CAS, are even scarcer. Given the toxicity of ICT and the rise of novel therapeutics, such as complement- and BTK-inhibitors, it is key to advance knowledge of ICT regimens in CAD and CAS.

Aims:

To assess real-world efficacy and tolerability of combined ICT for CAD/CAS.

Methods:

Clinical data were collected retrospectively for CAD/CAS patients, treated with R-bendamustine or R-cyclophosphamide-based therapy since 2000. Relevant Hb response was defined as a rise of ≥2.0 g/dl and/or to ≥12 g/dl. AEs were graded according to CTCAE v5.0. Event-free survival (EFS) was defined as time from start ICT until subsequent CAD/CAS treatment or death, with censoring at new therapy for underlying disease or end of follow-up. Data collection is ongoing.

Results:

Twenty-two patients from 11 Dutch hospitals were included. Median age at diagnosis was 63 years (IQR 53-70) and 13 (59%) were female. Underlying diagnoses were WM (n=8), IgM monoclonal gammopathy of undetermined significance (MGUS) (n=6), CLL (n=3), unspecified B-cell non-Hodgkin lymphoma (n=3) and CAD-LPD (n=2). Twenty-five ICT episodes were evaluated: 16 R-bendamustine and 9 R-cyclophosphamide-based regimens.

Of the 16 R-bendamustine treated patients, median follow-up (until next treatment, death or last follow-up) was 15.7 months (IQR 4.8-29.9). A relevant Hb response was reached in 12 patients (75%). Both transfusion dependent patients remained transfusion dependent. Median baseline Hb in the remaining 14 cases was 10.6 g/dl (IQR 9.5-12.1), with a median best Hb rise of 3.1 g/dL (IQR 1.1-4.0). Of 11 patients with acrocyanosis, 7 reported improvement, with complete resolution in 4. Median EFS was not reached. Six patients experienced grade ≥3 AEs, including 3 (febrile) neutropenia and 1 infection. Dose reductions were applied in 5.

Of the 9 DRC/RCP/R-CVP treated patients, median follow-up was 15.4 months (IQR 10.3-32.7). A relevant Hb response was reached in 6 patients. Both transfusion dependent patients remained transfusion dependent. Median baseline Hb in the remaining 7 cases was 8.9 g/dl (IQR 8.3-10.3), with a median best Hb rise of 3.7 g/dL (IQR: 2.7–4.3). Of 5 patients with acrocyanosis, 2 reported improvement, with complete resolution in 1. Median EFS was 15.4 months. Five patients experienced grade ≥3 AEs, including 4 (febrile) neutropenia and 2 infections. Dose reductions were applied in 3 cases and discontinuation in 1.

Summary/Conclusion:

Combined ICT may be beneficial for CAD/CAS patients, with a relevant Hb response in circa 70%, although transfusion dependence was not abolished in all 4 patients. Acrocyanosis improved in half of affected patients. In addition, ICT was associated with considerable incidence of high-grade toxicities.

FM and AB contributed equally to this work

Case	ICT type	Age at start ICT, *years*; sex	Underlying disease	Best Hb (baseline Hb), *g/dL*	CIPS at baseline; best response	Follow-up, *months*
1	RCP	82; F	Unspecified B-NHL	12.9 (7.9)	Yes; resolved	10 †
2	DRC	48; M	WM	12.9 (8.9)	Unknown	81 ^
3	DRC #	64; M	IgM MGUS	12.4 (10.2)	Unknown	35
4	DRC	73; F	WM	*NA, persistent transfusion dependence*	No	14 *
5	DRC #	66; M	IgM MGUS	*NA, persistent transfusion dependence*	No	5 *
6	DRC	54; F	CAD-LPD	11.3 (7.6)	Yes; improved	33
7	DRC	72; M	WM	13.2 (8.7)	Yes; no improvement	28 *
	R-benda	74; M	WM	15.0 (8.4)	Yes; resolved	29
8	R-CVP #	61; F	IgM MGUS	10.5 (11.6)	Yes; no improvement	8 *
	R-benda	76; F	IgM MGUS	11.8 (9.7)	Yes; no improvement	16
9	R-CVP #	78; M	WM	13.5 (10.5)	Yes; no improvement	15 *
	R-benda #	79; M	WM	13.2 (Unknown)	Yes; improved	15 ^
10	R-benda #	73; F	WM	16.1 (12.6)	Yes; improved	82
11	R-benda	79; F	CLL	13.5 (9.5)	Unknown	55
12	R-benda	63; F	CAD-LPD	10.8 (10.6)	Yes; no improvement	5
13	R-benda	69; F	Unspecified B-NHL	14.2 (9.8)	No	4
14	R-benda #	73; F	IgM MGUS	*NA, persistent transfusion dependence*	No	13 *
15	R-benda #	77; F	Unspecified B-NHL	10.2 (12.1)	Yes; no improvement	3
16	R-benda	65; F	WM	12.1 (9.0)	Yes; improved	4
17	R-benda	72; F	CLL	13.1 (8.9)	Yes; resolved	31
18	R-benda	72; F	IgM MGUS	15.1 (12.7)	Yes; resolved	27
19	R-benda	72; M	CLL	12.4 (12.9)	Yes; improved	6
20	R-benda	70; M	WM	*NA, persistent transfusion dependence*	Unknown	29 †
21	R-benda #	77; M	WM	12.6 (11.4)	No	4
22	R-benda	63; M	IgM MGUS	13.9 (10.6)	Yes; no improvement	61

B-NHL=B-cell non-Hodgkin lymphoma, CAD-LPD=cold agglutinin-associated lymphoproliferative disorder, CIPS=cold-induced peripheral symptoms, CLL=chronic lymphocytic leukemia, DRC=dexamethasone-rituximab-cyclophosphamide, F=female, Hb=hemoglobin level, ICT=immunochemotherapy, M=male, MGUS=monoclonal gammopathy of undetermined significance, R-benda=rituximab-bendamustine, RCP=rituximab-cyclophosphamide-prednisone, R-CVP=rituximab-cyclophosphamide-vincristine-prednisone, WM=Waldenström macroglobulinemia

Early discontinuation and/or dose reduction due to toxicities; * Follow-up ended due to start of new therapy for CAD/CAS; ^ Follow-up ended due to start of new therapy for underlying disease; † Follow-up ended due to death

Keywords: Bendamustine, Autoimmune hemolytic anemia (AIHA), Cyclophosphamide, Lymphoproliferative disorder