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Effective Treatment of Cold Agglutinin Disease/Cold Agglutinin Syndrome with Ibrutinib: An International Case Series

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Background

In cold agglutinin mediated autoimmune hemolytic anemia (cAIHA), anti-red blood cell autoantibodies lead to complement-mediated hemolysis with or without symptoms of acrocyanosis after exposure at low temperatures. cAIHA can be divided into cold agglutinin disease (primary CAD) and cold agglutinin syndrome (CAS). The latter is secondary to diseases such as B-cell malignancies including CLL, infections or autoimmune disorders. In primary CAD, more than 90% of patients have a monoclonal IgM (mostly low level) and often a small bone marrow B-cell clone. There is no approved treatment. For patients with significant hemolytic anemia or acrocyanosis despite thermal protection, rituximab is the most accepted first line treatment with an overall response rate of 50% and median duration of response <1 year. Cytotoxic combinations such as rituximab-bendamustine produce more sustained remissions, although with concerns for long-term adverse effects and stem cell toxicity. Studies involving complement inhibitors are showing promising results on hemolysis, although cold induced peripheral symptoms (IgM mediated rather than complement-mediated) will not improve. Recent international guidelines on cAIHA suggest treatment with the Bruton tyrosine kinase (BTK)-inhibitor ibrutinib in refractory patients with cAIHA (*Jäger et al Blood Rev 2020*). Indeed, the underlying pathophysiology of cAIHA suggest that BTK inhibition could be effective.

Aims

To evaluate the efficacy of ibrutinib on anemia, hemolysis and acrocyanosis in patients with cold agglutinin-mediated AIHA (CAD/CAS).

Methods

An international retrospective study was undertaken of cAIHA patients (CAD/CAS) treated with BTK inhibition using a preformed questionnaire. For eligible patients, laboratory and clinical data regarding underlying disease, bone marrow pathology, hemolytic parameters and patient-reported acrocyanosis were collected at diagnosis, 30 days, 3 months, 6 months and 12 months and last date of follow up. Hemoglobin

(Hb) response was considered none (NR), partial (PR, >2 g/dL Hb increase or >10g/dL) or complete (CR, >12g/dL). Adverse events were graded according to the Common Terminology Criteria, version-5.0 (2017).

Results

So far, 10 patients with cAIHA treated with a BTK-inhibitor (all involving ibrutinib) could be included in the study. Patients were followed from April 2014 until June 2020 at 5 centers (Italy (2), Norway, The United Kingdom and The United States). Median duration of follow up was 20 months (1-74 months). The main findings are summarized in table 1. The indication to start treatment was cAIHA based in all but 1 case (CLL). Median previous number of therapies was 2. All patients had a complement-mediated hemolytic anemia, 7 were transfusion-dependent, and 7 reported symptoms of acrocyanosis at the initiation of ibrutinib.

After initiation of ibrutinib, all patients showed an improvement in hemoglobin (Median rise: 4.4 g/dL) resulting in 1 PR and 9 CR. All 7 transfusion-dependent patients became transfusion independent (5 within 30 days). In all but 1 patient, markers of hemolysis (LDH, bilirubin) improved after initiation of ibrutinib (see Figure 1). All 7 patients with acrocyanosis reported clear clinical improvement, with complete resolution of symptoms in 5. There was 1 adverse event (grade 1 bleeding). Data collection is still ongoing and future updates are expected.

Conclusion

Data show that ibrutinib is effective in the treatment of cAIHA with a notable and brisk improvement of both the hemolytic anemia as well as the cold induced peripheral symptoms. Although preliminary, these promising data support further research of BTK-inhibitor based treatment of cAIHA (CAD/CAS) in a prospective study.

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Table 1. Baseline characteristics and treatment outcome

Case	Age in years	Bone marrow histology	MYD88 L265p mutation	Previous treatment	Hb (g/dL) at start	Transfusion dependent?	Duration of Ibrutinib treatment * (total months)	Acrocyanosis improved/ resolved	Date partial Hb response (Hb g/dL)**	Date complete Hb response** (Hb g/dL)	Rise in Hb (g/dL)
1	73	CLL	Na	Steroids IVIG	7.5	Yes	9	Na	30 days (11.9)	9 months (14.9)	7.4
2	66	CLL	Na	Steroids Rituximab Fludarabine	11.2	No	3	Na		30 days (12.2)	1
3	58	CLL	Na	No	8.8	Yes	4	Na		30 days (14.3)	5.5
4	67	CAD ass LPD	Negative	Rituximab Bendamustine Fludarabine	8.2	No	1	30 days: improved	30 days (10.5)		2.3
5	81	SLL	Na	Rituximab Bendamustine Bortezomib	6.9	Yes	21	30 days: improved, 3 months: resolved		3 months (13.5)	6.6
6	71	LPL/WM	Na	Steroids 6x DRC Rituximab	11.9	No	2	30 days: improved		30 days (12.7)	0.8
7	67	LPL/WM	Negative	Rituximab DRC Rituximab - maintenance	9.2	Yes	74	6 months: resolved		6 months (12.5)	3.3
8	66	LPL/WM	Negative	Rituximab	7.2	Yes	52	3 months: resolved	3 months (10.6)	6 months (12.0)	4.8
9	71	LPL/WM	Positive	No	8.2	Yes	51	30 days: resolved	30 days (10.0)	6 months (12.0)	3.8
10	55	LPL-WM	Positive	Steroids	5.9	Yes	3	30 days: resolved	30 days (10.7)	3 months (14.7)	8.8

Na: not applicable, CLL: chronic lymphatic leukemia, SLL: small lymphocytic lymphoma, LPD: lymphoproliferative disorder, LPL: lymphoplasmacytic lymphoma, WM: Waldenström macroglobulinemia, DRC: Dexamethasone, Rituximab, Cyclofosfamide, IVIG: intravenous immunoglobulin.
* All patients are still on Ibrutinib therapy
** Hb response considered partial (PR, >2 g/dL Hb increase or >10g/dL) or complete (CR, >12g/dL)

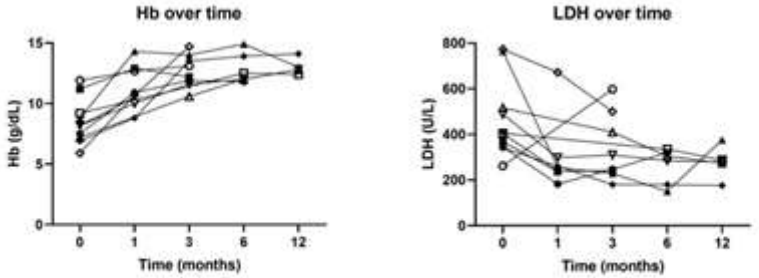

Figure 1. Hemoglobin (Hb) and LDH response over time

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Disclosures

Berentsen:*Alexion, Apellis, Bioverativ and Janssen-Cilag:* Other: Travel grants ; *Alexion, Apellis, Bioverativ, Janssen-Cilag, True North Therapeutics:* Honoraria; *Apellis, Bioverativ, Momenta Pharmaceuticals and True North Therapeutics:* Consultancy; *Mundipharma:* Research Funding**. Castillo:***TG Therapeutics:* Research

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OffLabel Disclosure:

BTK-inhibitors (ibrutinib/acalabrutinib) are not yet indicated for the use in (primairy) cold autoimmune hemolytic anemia (cAIHA). However it is indicated for use in Waldenstrom macroglobulinemia (WM) and chronic lymphatic leukemia (CLL). Here we report retrospective data on a cohort of cases treated with ibrutinib for cAIHA mostly secondary to WM or CLL.

Author notes

* Asterisk with author names denotes non-ASH members.

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