Management of atypical localization of chronic lymphocitic leukemia treated with venetoclax plus obinutuzumab

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REVOLUTIONARY ROAD IN CLL

Innovazione rivoluzionaria nella terapia della leucemia linfatica cronica

Padova, 22 maggio 2024
Hotel NH Padova

Disclosures

Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other
AstraZeneca							x
Beigene						x	

Clinical presentation

Patient: Roberto, male, 36 **years**
Comorbidities: none; *Drugs*: none
Physiological history: no smoker, no allergies
Clinical: worsening asthenia, insomnia, sleep apnea → medical evaluation

February 2023

CBC: WBC 37.500/mmc, ANC 4.000/mmc, ALC 42.300/mmc, Hb 14.6 g/dl, Plts 179.000/mmc
Exams: glucose, creatinine (0.98 mg/dL), elettrolites, liver function, LDH (466 UI/L) and BUN (6.3 mg/dL) in range
Immunofenotype: conclusive for Chronic Lymphocitic Leukemia
Biological profile: IGHV unmutated, TP53 wild type, FISH positive for del13q, negative for del17p, del11q, tris12
ENT visit: indication for tonsillar biopsy for suspected localization of lymphoproliferative disease.

March 2023

Histological tonsillar biopsy: small lymphocyte lymphoma.
CT scan: bilateral axillary lymphnodes (38 mm on the right, 26 mm on the left); laterocervical and bilateral submandibular lymphnodes (max 23 mm on the right); mild splenomegaly (DL 15 cm); left inguinal lymphnode (19x14 mm).
Haematological evaluation: histological confirmation of tonsillar CLL in young man with clinical presentation of sleep apnea

May 2023

→ *watch and wait or start 1st line treatment*?

Tonsillar localization of CLL/SLL

virtually any lymphoid tissue may be enlarged at diagnosis, including Waldeyer's ring in the pharynx

but it is not frequent as treatment criterion!!

Ottinger AM, et al. Ear Nose Throat J. 2023 Nov 24:1455613231214634. doi: 10.1177/01455613231214634. Unilateral Tonsillar Enlargement as Initial Presentation of Bilateral Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma.

Duggal R, et al. Case Reports Indian J Hematol Blood Transfus. 2016 Jun;32(Suppl 1):152-5. doi: 10.1007/s12288-015-0629-8. Epub 2015 Dec 11. Bilateral Tonsillar Enlargement as a First Manifestation of Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma with an Unusual Interfollicular Pattern of Infiltration

Prabhjot Kaur, Tipu Nazeer. Am J Otolaryngol. 2004 Mar-Apr;25(2):121-5. doi: 10.1016/j.amjoto.2003.09.009. B-cell chronic lymphocytic leukemia/small lymphocytic lymphoma presenting in the tonsil: a case report and review of literature

Options – may 2023

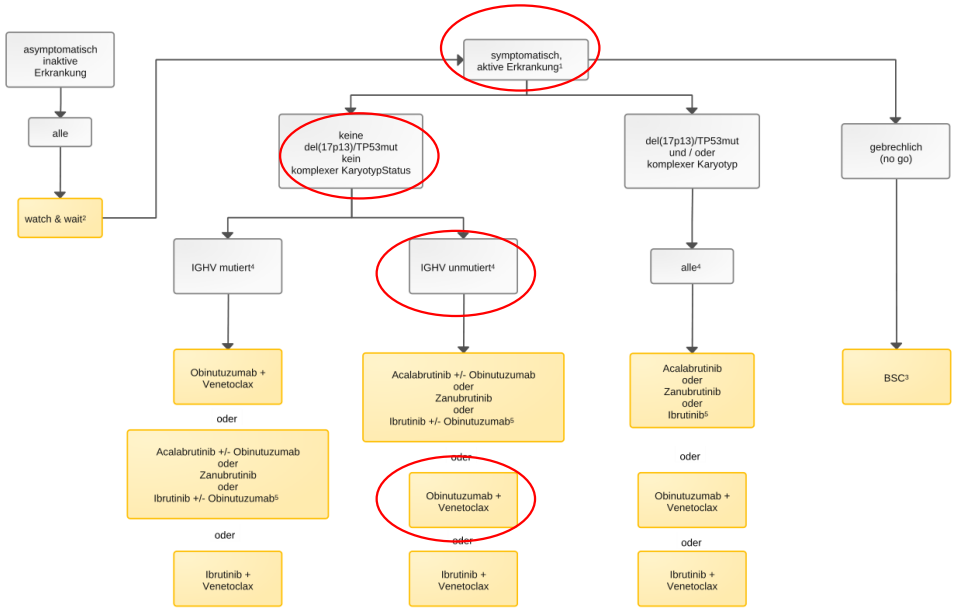
Watch and wait

Continuous therapy:
first or second generation Bruton Tyrosine Kinase Inhibitors
(ibrutinib or acalabrutinib)

Fixed duration therapy:
obinutuzumab plus venetoclax

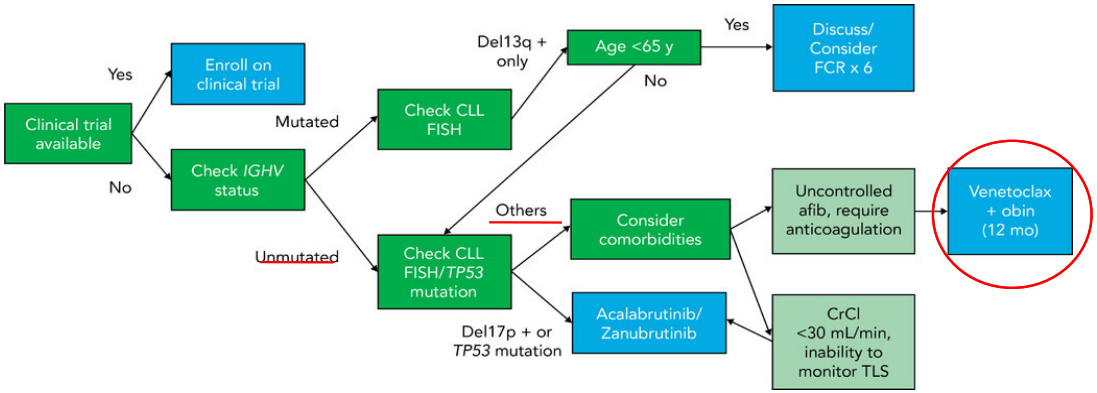
Treatment choice

ONKOPEDIA 2023



Onkopedia guidelines update: Clemens-Martin Wendtner, Othman Al-Sawaf, Mascha Binder, et al. Chronische Lymphatische Leukämie (CLL).

NCCN 2023



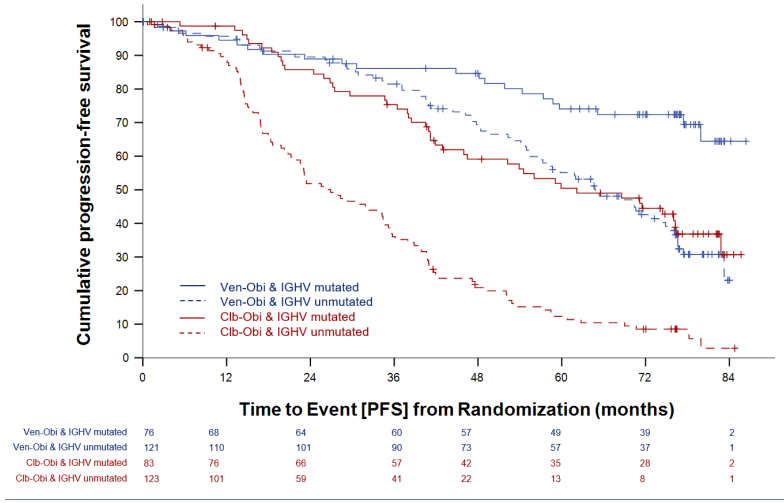
NCCN Guidelines Update: Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma. J Natl Compr Canc Netw. 2023;21(5.5):563-566

Treatment choice

CLL14 6-year update

PROGRESSION-FREE SURVIVAL – IGHV status

Median observation time 76.4 months



Median PFS

Ven-Obi & IGHVmut: NR

Ven-Obi & IGHVunmut: 64.8 m

HR 0.38, 95%CI [0.23-0.61], p<0.001

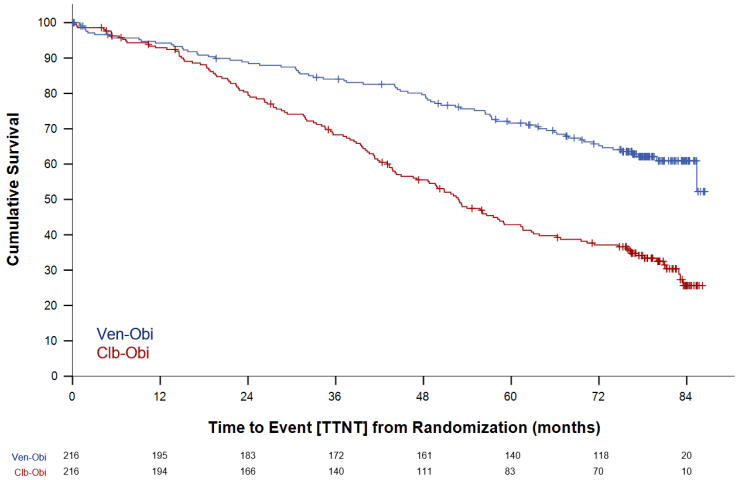
Clb-Obi & IGHVmut: 62.2 m

Clb-Obi & IGHVunmut: 26.9 m

HR 0.33, 95% CI [0.23-0.47], p<0.001

TIME TO NEXT TREATMENT

Defined as time to death or next-antileukemic treatment



Median TTNT

Ven-Obi: not reached

Clb-Obi: 52.9 m

6-year TTNT rate

Ven-Obi: 65.2%

Clb-Obi: 37.1%

Next anti-leukemic therapy:

Ven-Obi: 67 PDs – 39 NLT

Clb-Obi: 141 PDs – 103 NLT

HR 0.44, 95% CI [0.33-0.58]

P<0.0001

Al-Sawaf O, et al. EHA 2023. Abstract S145 (Oral).

Treatment choice

Age → young → **fixed >>>** continous

Comorbidities → none → **fixed = continuous**

Clinical disease → blood and nodal, no bulky → **fixed = continuous**

Biological disease → IGHV UNM, TP53 WT, no del17p → continuous **>** fixed? Not relevant!

Patient opinion → young/work/life style → **fixed >>>** continuous

Treatment - Day Hospital
Obinutuzumab

June, 05th 23

Start

→ Infusion related reaction (IRR) on C1D1

Heat and hypotension resolved with steroids and IV fluids

→ Laboratory tumor lysis syndrome (TLS risk: intermediate)

ALC before treatment 37500/mmc, no lymphadenopathies >5 cm, no splenomegaly

Hyperuricemia prophylaxis with allopurinolo; IV fluids

→ Rapid resolution of clinical treatment criteria

Treatment - Day Hospital
Venetoclax

June, 26th 23
Start

→ No complications

→ No TLS

→ No discontinuation

Evaluation

→ *Immunofenotype (december 2023, march 2024, may 2024):* negative

→ *ENT visit (march 2024)*: clinical response

→ *CT scan june 2024*

Safety concerns

Table S6. Overview of adverse events with an incidence rate of ≥10% of patients in either treatment group (safety population).

Adverse events	Venetoclax–obinutuzumab (N=212)	Chlorambucil–obinutuzumab (N=214)
At least one adverse event – no. of patients (%)	200 (94.3)	213 (99.5)
Adverse events with an incidence rate of ≥10% in any treatment group – no. of patients (%)		
Blood and lymphatic system disorders	145 (68.4)	137 (64.0)
Neutropenia*	122 (57.5)	122 (57.0)
Thrombocytopenia	51 (24.1)	50 (23.4)
Anemia	35 (16.5)	40 (18.7)
Injury, poisoning, and procedural complications	95 (44.8)	110 (51.4)
Infusion-related reaction	95 (44.8)	110 (51.4)
Gastrointestinal disorders	89 (42.0)	74 (34.6)
Diarrhea	59 (27.8)	32 (15.0)
Nausea	40 (18.9)	46 (21.5)
Constipation	28 (13.2)	19 (8.9)
General disorders and administration site conditions	68 (32.1)	60 (28.0)
Pyrexia	48 (22.6)	33 (15.4)
Fatigue	32 (15.1)	30 (14.0)
Respiratory, thoracic, and mediastinal disorders	34 (16.0)	25 (11.7)
Cough	34 (16.0)	25 (11.7)
Nervous system disorders	24 (11.3)	21 (9.8)
Headache	24 (11.3)	21 (9.8)

Adverse events are reported by *Medical Dictionary for Regulatory Activities* (MedDRA) superclass and preferred terms and NCI CTCAE grade.

* GCSF could be administered at the discretion of the treating physician according to local practice

Table 2. Grade 3 or 4 Adverse Events (Safety Population).*

Adverse Event	Venetoclax–Obinutuzumab (N=212)†			Chlorambucil–Obinutuzumab (N=214)		
	Maximum Grade 3	Maximum Grade 4	Maximum Grade 3 or 4	Maximum Grade 3	Maximum Grade 4	Maximum Grade 3 or 4
	number of patients (percent)					
Adverse event of grade 3 or 4	81 (38.2)	86 (40.6)	167 (78.8)	93 (43.5)	71 (33.2)	164 (76.6)
Adverse events of grade 3 or 4 that occurred in ≥3% of the patients in either treatment group‡						
Blood and lymphatic system disorders	59 (27.8)	69 (32.5)	128 (60.4)	61 (28.5)	57 (26.6)	118 (55.1)
Neutropenia	52 (24.5)	60 (28.3)	112 (52.8)	56 (26.2)	47 (22.0)	103 (48.1)
Thrombocytopenia	20 (9.4)	9 (4.2)	29 (13.7)	19 (8.9)	13 (6.1)	32 (15.0)
Anemia	16 (7.5)	1 (0.5)	17 (8.0)	13 (6.1)	1 (0.5)	14 (6.5)
Febrile neutropenia	7 (3.3)	4 (1.9)	11 (5.2)	4 (1.9)	4 (1.9)	8 (3.7)
Leukopenia	5 (2.4)	0	5 (2.4)	9 (4.2)	1 (0.5)	10 (4.7)
Infections and infestations	31 (14.6)	6 (2.8)	37 (17.5)	31 (14.5)	1 (0.5)	32 (15.0)
Pneumonia	8 (3.8)	1 (0.5)	9 (4.2)	8 (3.7)	0	8 (3.7)
Injury, poisoning, and procedural complications	21 (9.9)	5 (2.4)	26 (12.3)	29 (13.6)	1 (0.5)	30 (14.0)
Infusion-related reaction	16 (7.5)	3 (1.4)	19 (9.0)	21 (9.8)	1 (0.5)	22 (10.3)
Investigations	26 (12.3)	6 (2.8)	32 (15.1)	16 (7.5)	7 (3.3)	23 (10.7)
Neutrophil count decreased	7 (3.3)	2 (0.9)	9 (4.2)	4 (1.9)	6 (2.8)	10 (4.7)
Aspartate aminotransferase increased	5 (2.4)	0	5 (2.4)	7 (3.3)	0	7 (3.3)
Alanine aminotransferase increased	4 (1.9)	0	4 (1.9)	7 (3.3)	0	7 (3.3)
Metabolism and nutrition disorders§	19 (9.0)	6 (2.8)	25 (11.8)	11 (5.1)	1 (0.5)	12 (5.6)
Hyperglycemia	6 (2.8)	2 (0.9)	8 (3.8)	2 (0.9)	1 (0.5)	3 (1.4)
Gastrointestinal disorders ¶	16 (7.5)	1 (0.5)	17 (8.0)	6 (2.8)	1 (0.5)	7 (3.3)
Diarrhea‖	9 (4.2)	0	9 (4.2)	1 (0.5)	0	1 (0.5)
Cardiac disorders	9 (4.2)	1 (0.5)	10 (4.7)	10 (4.7)	2 (0.9)	12 (5.6)
Neoplasms benign, malignant, and unspecified, including cysts and polyps	10 (4.7)	3 (1.4)	13 (6.1)	7 (3.3)	1 (0.5)	8 (3.7)
Vascular disorders**	12 (5.7)	2 (0.9)	14 (6.6)	7 (3.3)	0	7 (3.3)
General disorders and administration-site conditions ††	14 (6.6)	0	14 (6.6)	6 (2.8)	0	6 (2.8)

Fischer K, et al. N Engl J Med 2019

Options – may 2024

Watch and wait

Continuous therapy
first or second generation Bruton Tyrosine Kinase Inhibitors
(ibrutinib or acalabrutinib or zanubrutinib)

Fixed duration therapy
obinutuzumab plus venetoclax
ibrutinib plus venetoclax

Options – may 2025?


That's all Folks!