# Treatment of symptomatic paraneoplastic fluidothorax in CLL with novel agents: a single-center case series

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## INTRODUCTION

Chronic lymphocytic leukemia (CLL) is presenting with various clinical manifestations. CLL cells are mainly present in the peripheral blood, bone marrow and lymph nodes. As a rare compartment involvement could be a pleural space. We describe here a case series of four patients (P1-P4; characteristics are summarised in Fig.1) with symptomatic CLL paraneoplastic fluidothorax, successfully treated by novel agents.

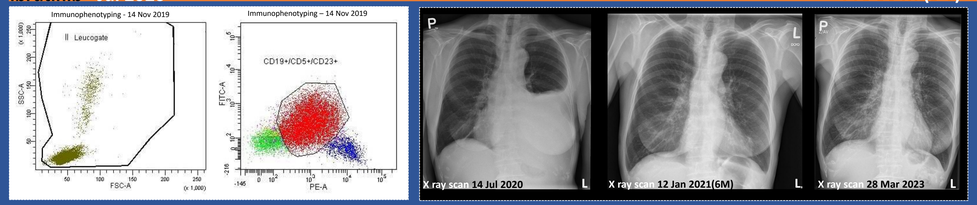
## PATIENTS AND CASES DESCRIPTION

**P1** Woman, born in 1941, CLL diagnosed in 2018 (in 77 years), stadium Binet B, Rai I., *IGHV* unmutated, *del 6q*. CIRS (Cumulative Illness Rating Scale): 8 (facial herpes zoster, residual paresis of ocular nerves, dyslipidemia, hypertension, osteoporosis).

I.st line (L): 6 x RCD (rituximab, cyclophosphamide, dexamethasone), Nov 2019 to Apr 2020 due to symptomatic fluidothorax - partial remission of fluidothorax (PRF)

II. nd L: reduced **ibrutinib** (140 mg/day) started July 2020, - complete regression of fluidothorax (CRF), follow up (FU) Jun 2023

**ibrutinib - Jul 2020** → **PFS 36 M (3 Y)**







**P2** Man, born in 1948, CLL diagnosed in 2012 (in 64 years), *del 11q, IGHV* mutated. CIRS: 9 (ischemic cardiac disease, atrial fibrillation, hypertension, hyperuricemia)

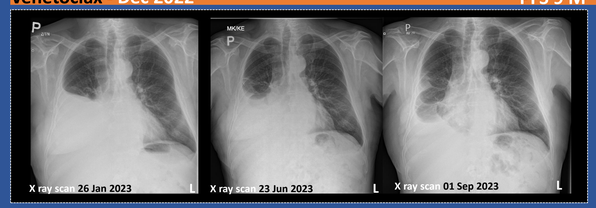
I.st L: 6 x FCR (fludarabine, cyclophosphamide, rituximab) Nov 2013 to Apr 2013 - complete remission (CR 1), relaps - Sep 2016

II.nd L: 5 x FCR, Feb to Aug 2017 - CR 2

III.rd L: R-idelalisib, Dec 2018 - Nov 2022 – progressive disease (PD) - symptomatic fluidothorax (fluidothorax and pleura infiltration verified by immunophenotyping and histology)

IV.th L: venetoclax since Dec 2022, partial remission of fluidothorax, FU Sep 2023 (PFS 9 months)

**venetoclax - Dec 2022** → **PFS 9 M**




## RESULTS AND CONCLUSION

We present two patients where fluidothorax was observed at the time of diagnosis and two patients who developed fluidothorax after prior therapies. Fluidothoraxes were in two patients sensitive to ibrutinib and in two patients to venetoclax (refractory to idelalisib). Only one patient progressed during FU to Richter transformation. Two patients received ICT as first line treatment and were refractory. In two patients, fluidithorax developed at idelalisib treatment. Although the number of patients presented is too small to conclude on the best treatment choice for CLL-related fluidothorax, it seems that BTK inhibitors and BCL2 inhibitors could be an effective choice.

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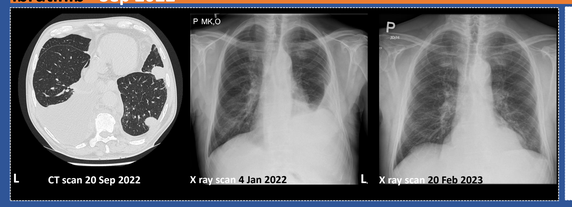
**P3** Man, born in 1951, CLL diagnosed in March 2020 (in 69 years), *IGHV* unmutated, 46 XY, CIRS: 8 (diabetes mellitus, diabetic foot disease, lower extremity ischemic disease)

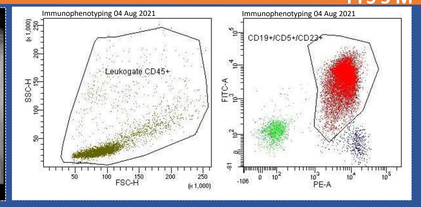
I.st L: 1 x RCD, 3 x R- bendamustine, Aug 2021 to Nov 2021 due to generalised lymphadenomegalia (LAM) - in retroperitoneal space up to 42 mm, fluidothorax and B symptoms), stopped due to infection – PRF

II.nd L: ibrutinib, Sep 2022 (due to progressive lymphadenomegaly(LAM) and fluidothorax (70% CLL infiltration), best response to January 2023 – CRF, LAM remission, Feb 2023 – PD (abdominal LAM, Richter transformation)

III.rd L: 2 x R-CHOP, Apr 2023 to May 2023, PD – died May 2023

**ibrutinib - Sep 2022** → **PFS 5 M**




**P4** Man, born in 1969, CLL diagnosed in Mar 2017 (in 48 years), *IGHV* unmutated, *del 11q, del 13q*, CIRS: 2 (hypertension)

I.st L: 3 x RCD, 2x FCR, Dec 2017 to Apr 2018 (due to cytopenia and LAM) – PD

II.nd L: R-idelalisib, Jun 2018 to Jun 2022, PD - massive LAM, bone lesions, cytopenia, symptomatic fluidothorax, (*TP53* mutation)

III.rd L: 1 x RCD, venetoclax, since Jun 2022, CR+CRF. FU Aug 2023 (PFS 14 months)

**venetoclax - Jun 2022** → **PFS 14 M**

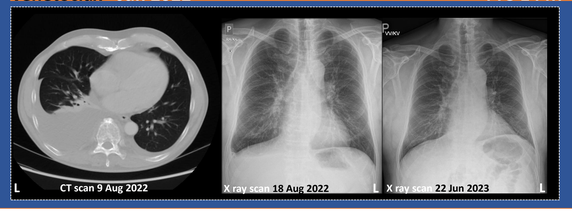



**Fig.1: Patients, fluidithorax and treatment characteristics**

| PATIENT | P1 | P2 | P3 | P4 |
|---|---|---|---|---|
| Sex | F | M | M | M |
| Age at fluidothorax diagnosis | 78 | 74 | 70 | 53 |
| *IGHV* mutation status | U | M | U | U |
| Genetics | *del 6q* | *del 11q* | *46 XY* | *del 11q, 13q, TP53 mut.* |
| Time to first treatment (months) | 13 | 12 | 17 | 1 |
| Lymphadenopathy greater than 2 cm | N | N | Y | N |
| Lymphocytosis > 50x10.9/l at fluidothorax diagnosis/progression | N | N | N | N |
| CLL cells in fluidothorax - % (cytometry) | 60 | Na | 70 | NA |
| Therapy lines | 2 | 4 | 2 | 3 |
| Progression at therapy | ICT | R-idelalisib | ICT | R-idelalisib |
| Sensitive to therapy | ibrutinib | venetoclax | ibrutinib | venetoclax |
| Fluidithorax regression response | complete | partial | complete | complete |
| PFS (months) | 36 | 9 | 5 | 14 |

**M**-male; **F**-female; **ICT** – imunochemotherapy