Minimal Residual Disease in Untreated, Physically Fit Chronic Lymphocytic Leukaemia (CLL) Patients: Results of a Systematic Review with Bayesian Network Meta-Analysis

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Introduction

Background

Chronic lymphocytic leukemia (CLL) is a rare form of cancer that primarily affects the blood and bone marrow [1, 2]. Despite its rarity, CLL is the most common type of leukemia in Europe, with an age-standardized incidence rate of approximately 3 per 100,000 people in 2019 [3]. It occurs predominantly in older adults, making age one of the major risk factors. Additionally, the disease is characterized by extensive genetic and molecular heterogeneity, resulting in substantial variability among patients in terms of clinical presentation, treatment response, and prognosis [1].

For treatment-naïve CLL (TN-CLL) patients who require therapy, a critical factor in therapeutic decision-making is the patient's overall fitness level [1]. Based on this, the TN-CLL population is divided into two subgroups: fit and unfit patients. The fit subgroup includes those eligible for more intensive treatments, such as fludarabine-based chemotherapy, including the fludarabine + cytarabine + rituximab regimen. Conversely, the unfit subgroup consists of patients who are not candidates for fludarabine due to factors such as age, comorbidities, or impaired renal function, which limit their ability to tolerate the potential toxicity associated with more intensive chemotherapy [1].

Targeted therapies represent a significant advancement in the treatment of not only unfit patients but also physically fit patients with TN-CLL. These therapies have the potential to improve outcomes, particularly in terms of reducing minimal residual disease (MRD), which is an important prognostic marker for both progression-free survival and overall survival [4–6]. However, despite the growing use of these therapies, there is a gap in the understanding of their relative efficacy, especially in achieving undetectable MRD in peripheral blood (MRD(-)PB) among physically fit patients with TN-CLL.

Objective

The aim of this study was to compare the odds of achieving MRD(-)PB between different targeted therapies in physically fit patients with TN-CLL, using a Bayesian network meta-analysis (NMA).

Methods

Systematic Literature Review

A systematic review of the literature was conducted to identify randomized clinical trials focusing on fit patients with TN-CLL. The search involved major medical databases such as MEDLINE, EMBASE, and CENTRAL, as well as additional sources such as the websites of oncological and hematological societies (e.g., European Hematology Association) and clinical trial registries (e.g., EU Clinical Trials Register). The websites of regulatory agencies, such as the European Medicines Agency, were also reviewed. The last search of major medical databases was conducted on May 23, 2023.

The systematic review was registered in the PROSPERO database (CRD42023393903) and was conducted in accordance with the PRISMA and PRISMA-NMA guidelines [7, 8].

Network meta-analysis

A Bayesian NMA was conducted to evaluate the relative efficacy of the selected therapeutic options in terms of MRD(-)PB. The analysis followed NICE guidelines (NICE DSU TSD[9]) and was performed using the WinBugs and R software.

Data from the most similar and longest available duration follow-up were used to compare MRD(-)PB.

Results from the fixed-effects model were expressed as odds ratios (OR) with 95% credible intervals (95% CrI). Additionally, the surface under the cumulative ranking curve (SUCRA) value for each therapeutic option was calculated.

Results

Search results

The systematic review identified 6 randomized clinical trials (E1912 [10–20], FILO [21–23] FLAIR [24–29], CLL8 [30–43], CLL10 [44–54], and CLL13 [GAIA] [55–59]) reporting MRD(-)PB data for the fit population with TN-CLL.

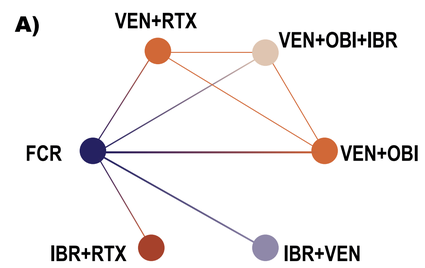
Efficacy results

The analysis of MRD(-)PB from studies with the most similar follow-up duration showed that venetoclax + obinutuzumab + ibrutinib significantly outperformed other targeted therapies such as venetoclax + rituximab, venetoclax + obinutuzumab, ibrutinib + rituximab, and ibrutinib + venetoclax (Fig. 1A).

Similar results were obtained in the analysis of the longest available follow-up (Fig. 1B).

In both analyses, venetoclax + obinutuzumab + ibrutinib showed the highest SUCRA values (the best treatment option) (Fig. 1 A-B).

Figure 1. Results of network meta-analysis (odds ratios and SUCRA values) and network geometry for undetectable MRD in peripheral blood



A) Undetectable MRD in peripheral blood - analysis for the most similar follow-up

	FCR	VEN+OBI+IBR	VEN+OBI	VEN+RTX	IBR+RTX	IBR+VEN
FCR	-	**0.11 [0.05, 0.22]**	**0.25 [0.14, 0.44]**	1.21 [0.77, 1.93]	**14.58 [10.14, 21.44]**	1.08 [0.51, 2.27]
VEN+OBI+IBR	**8.7 [4.46, 18.55]**	-	**2.21 [1.04, 4.94]**	**10.58 [5.46, 22.38]**	**127.8 [59.24, 295.77]**	**9.43 [3.43, 27.06]**
VEN+OBI	**3.94 [2.27, 7.03]**	**0.45 [0.2, 0.96]**	-	**4.79 [2.78, 8.51]**	**57.7 [29.72, 115.02]**	**4.25 [1.67, 10.91]**
VEN+RTX	0.82 [0.52, 1.3]	**0.09 [0.04, 0.18]**	**0.21 [0.12, 0.36]**	-	**12.03 [6.65, 21.74]**	0.89 [0.37, 2.13]
IBR+RTX	**0.07 [0.05, 0.1]**	**0.01 [0, 0.02]**	**0.02 [0.01, 0.03]**	**0.08 [0.05, 0.15]**	-	**0.07 [0.03, 0.17]**
IBR+VEN	0.93 [0.44, 1.97]	**0.11 [0.04, 0.29]**	**0.24 [0.09, 0.6]**	1.13 [0.47, 2.71]	**13.58 [5.9, 31.28]**	-
SUCRA	48%	100%	80%	32%	0%	41%

B) Undetectable MRD in peripheral blood - analysis for the longest follow-up

	FCR	VEN+OBI+IBR	VEN+OBI	VEN+RTX	IBR+RTX	IBR+VEN	BEND+RTX	FC
FCR	-	**0.11 [0.05, 0.22]**	**0.25 [0.14, 0.44]**	1.21 [0.77, 1.92]	**5.13 [2.67, 10.6]**	0.93 [0.44, 1.96]	**1.52 [1.09, 2.13]**	**3.7 [2.43, 5.82]**
VEN+OBI+IBR	**8.8 [4.48, 18.55]**	-	**2.23 [1.05, 4.97]**	**10.69 [5.51, 22.4]**	**45.45 [17.56, 127.31]**	**8.22 [3, 23.49]**	**13.4 [6.31, 30.33]**	**32.72 [14.7, 77.52]**
VEN+OBI	**3.94 [2.28, 7.02]**	**0.45 [0.2, 0.95]**	-	**4.79 [2.78, 8.5]**	**20.26 [8.58, 50.97]**	**3.67 [1.45, 9.45]**	**6 [3.15, 11.7]**	**14.65 [7.26, 30.33]**
VEN+RTX	0.82 [0.52, 1.3]	**0.09 [0.04, 0.18]**	**0.21 [0.12, 0.36]**	-	**4.23 [1.9, 9.91]**	0.77 [0.32, 1.84]	1.25 [0.71, 2.22]	**3.05 [1.62, 5.8]**
IBR+RTX	**0.2 [0.09, 0.37]**	**0.02 [0.01, 0.06]**	**0.05 [0.02, 0.12]**	**0.24 [0.1, 0.53]**	-	**0.18 [0.06, 0.49]**	**0.3 [0.13, 0.62]**	0.72 [0.31, 1.6]
IBR+VEN	1.07 [0.51, 2.27]	**0.12 [0.04, 0.33]**	**0.27 [0.11, 0.69]**	1.31 [0.54, 3.14]	**5.54 [2.04, 15.59]**	-	1.64 [0.72, 3.7]	**3.99 [1.68, 9.52]**
BEND+RTX	**0.66 [0.47, 0.92]**	**0.07 [0.03, 0.16]**	**0.17 [0.09, 0.32]**	0.8 [0.45, 1.41]	**3.37 [1.61, 7.47]**	0.61 [0.27, 1.39]	-	**2.44 [1.42, 4.27]**
FC	**0.27 [0.17, 0.41]**	**0.03 [0.01, 0.07]**	**0.07 [0.03, 0.14]**	**0.33 [0.17, 0.62]**	1.38 [0.63, 3.2]	**0.25 [0.1, 0.6]**	**0.41 [0.23, 0.71]**	-
SUCRA	60%	100%	86%	47%	3%	60%	33%	11%

BTK+Immunotherapy · BCL-2+immunotherapy · BCL-2+immunotherapy+BTK · BCL2+BTK · Chemoimmunotherapy · Chemotherapy

Data presented as OR [95% CrI]; FC(R) – fludarabine + cyclophosphamide + (rituximab); VEN – venetoclax; OBI – obinutuzumab; IBR – ibrutinib; RTX – rituximab; BEND – bendamustine; MRD- minimal residual disease; BTKi - Bruton's tyrosine kinase inhibitor; BCL-2i - B-cell lymphoma 2 inhibitor.

Conclusions

The NMA results revealed that venetoclax + obinutuzumab + ibrutinib was the most effective therapeutic option for improving the odds of MRD(-)PB. However, further research is necessary to confirm these findings.

LIMITATION: *Data for ibrutinib + venetoclax come from the FILO study, which was published as a conference abstract.*

References

1. Annals of Oncology 32(1):23–33.
2. https://rarediseases.org/rare-diseases/chronic-lymphocytic-leukemia/ (18.9.2023).
3. Front Oncol 12:840616.
4. JHPOR (2):2–10.
5. Curr Oncol Rep 26(2):136–146.
6. Blood 142(Supplement 1):1901.
7. BMJ 372:n71.
8. Ann Intern Med 162(11):777–784.
9. https://www.sheffield.ac.uk/media/34176/download?attachment.
10. https://www.ema.europa.eu/documents/product-information/imbruvica-epar-product-information_en.pdf.
11. https://www.ema.europa.eu/en/documents/variation-report/imbruvica-h-c-3791-ii-0059-epar-assessment-report-variation_en.pdf.
12. New England Journal of Medicine 381(5):432–443.
13. Blood 140(2):112–120.
14. Blood 138(26):2810–2827.
15. Blood 128(22):4373.
16. Blood 130:4288.
17. Blood 132:236.
18. Blood 138:1562.
19. Blood 132(Supplement 1):LBA-4.
20. Blood 134:33.
21. Blood 138(Supplement 1):641.
22. Leukemia & lymphoma (62):86–87.
23. Blood (140 (Supplement 1)):7007–7009.
24. British journal of haematology (197):16–17.
25. Blood 138:2636.
26. Trials 22(38):1–13.
27. Lancet Oncol 24(5):535–552.
28. Blood 138:642.
29. Trials 18(1):387.
30. Blood 112(11):326.
31. J Clin Oncol 30(9):980–988.
32. Blood 114(22):3438.
33. Clinical Lymphoma Myeloma and Leukemia 11:S230.
34. Blood 120(21):435.
35. Oncology Research and Treatment (37):86.
36. Blood 127(2):208–215.
37. Blood 114(22):535.
38. Lancet 376(9747):1164–1174.
39. Leuk Lymphoma 58(2):399–407.
40. Blood 124(21):1938.
41. Expert Rev Anticancer Ther 11(9):1333–1340.
42. Blood 114(22):1267.
43. Blood (118):2863.
44. Blood 122(21):526.
45. Blood 124(21):19.
46. Blood 128(22):4382.
47. Lancet Oncol 17(7):928–942.
48. Blood 130:3021.
49. HemaSphere 4(1):e336.
50. Oncology Research and Treatment 37:185.
51. Haematologica (99(s1)):55–56.
52. https://www.clinicaltrialsregister.eu/ctr-search/rest/download/result/zip/pdf/2007-007587-21/1.
53. https://clinicaltrials.gov/ct2/show/results/NCT00281918.
54. Onkologie (34 (suppl 6)):142.
55. Blood 138:71.
56. Blood 138:2639.
57. N Engl J Med 388(19):1739–1754.
58. Blood 138:72.
59. JCO 36(15_suppl):TPS7582–TPS7582.

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