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Comparative Bayesian Network Meta-Analysis of BTKi-Specific Adverse Events in Patients With Relapsed/Refractory Chronic Lymphocytic Leukemia

Monica Magdalena[1], Reczek Monika[2], Kawalec Pawel[3]

[1]Doctoral School of Medical and Health Sciences, Jagiellonian University Medical College, Cracow, Poland; [2]HTA Consulting, Cracow, Poland; [3]Jagiellonian University Medical College Institute of Public Health, Cracow, Poland

INTRODUCTION

- Bruton kinase inhibitors (BTKi), including ibrutinib, acalabrutinib, and zanubrutinib, are effective treatments for relapsed/refractory chronic lymphocytic leukemia (R/R CLL)[1-3]
- Recent findings suggest that they may increase the risk of cardiovascular adverse events, including hypertension, atrial fibrillation, and bleeding[1-3]

OBJECTIVE

- The study aimed to compare the risk of cardiovascular events between possible therapies for relapsed/refractory CLL using statistical methods of Bayesian network meta-analysis (NMA)
- The analyzed therapies included chemotherapy (bendamustine), immunotherapy (ofatumumab, rituximab, ublituximab), Bruton kinase inhibitors (acalabrutinib, ibrutinib, zanubrutinib), and PI3K inhibitors (idelalisib), which were used as monotherapy or in combination with other agents

METHODS

SYSTEMATIC LITERATURE REVIEW

- On October 10, 2023, we performed a systematic search (CRD42022304330) for randomized clinical trials conducted in patients with relapsed/refractory disease who previously received at least one treatment line
- Searched sources included medical databases (MEDLINE, EMBASE, CENTRAL), clinical trials registries (e.g., ClinicalTrials.gov), conference proceedings of hematological and oncological societies (e.g., ASCO), websites of medicines regulatory authorities (e.g., EMA) and health-technology assessment agencies (e.g., NICE)
- The systematic review was performed in agreement with PRISMA guidelines and their extension for network meta-analyses (NMA)[4,5]

NETWORK META-ANALYSIS

- We performed Bayesian NMAs to synthesize direct and indirect evidence for relapsed/refractory CLL
- Data for the longest follow-up from the identified by systematic search studies were used to compare the risk of atrial fibrillation, bleeding, and hypertension
- All analyses were performed using a fixed model and GeMTC package for R software
- The results of NMA were presented as risk ratios (RR) with 95% credible intervals (CrI)
- SUCRA values were also calculated for each treatment

RESULTS

HYPERTENSION

- 7 studies (ALPINE[1], ASCEND[2], Burger 2019[6], ELEVATE-RR[7], GENUINE[8], HELIOS[9-10], Huang 2018[11]) reporting hypertension were found as a result of the systematic search
- Among BTKis, ibrutinib and zanubrutinb demonstrated a significantly higher risk of hypertension compared to acalabrutinib
- Patients treated with acalabrutinib showed lower rates of grade ≥3 hypertension compared to ibrutinb, ibrutinib+rituximab, and zanubrutinib
- Bendamustine+rituximab demonstrated the lowest probability of hypertension (SUCRA: 0.96)

Overall hypertension (all grades)

Grade ≥3 hypertension								
ACA	0.26 [0.01; 1.49]	2.66 [1.72; 4.27]	0.51 [0.02; 3.23]	2.39 [1.41; 4.18]	3.41 [1.21; 10.08]	0.75 [0.28; 1.82]	2.49 [0.48; 10.23]	2.96 [1.74; 5.16]
2.17 [0.34; 60.61]	BEND+RTX	10.27 [1.68; 271.80]	1.96 [1.15; 3.47]	9.26 [1.48; 246.29]	13.45 [1.68; 399.35]	2.85 [0.45; 76.22]	9.89 [0.84; 308.12]	11.47 [1.80; 304.51]
0.47 [0.22; 0.92]	0.21 [0.01; 1.55]	IBR	0.19 [0.01; 1.28]	0.90 [0.66; 1.21]	1.27 [0.50; 3.41]	0.28 [0.09; 0.76]	0.94 [0.19; 3.53]	1.11 [0.82; 1.50]
0.64 [0.06; 19.87]	0.29 [0.08; 0.84]	1.40 [0.13; 46.25]	IBR+BEND+RTX	4.75 [0.69; 128.91]	6.89 [0.80; 206.48]	1.46 [0.21; 40.41]	5.05 [0.40; 164.24]	5.85 [0.84; 159.66]
0.45 [0.19; 0.999]	0.20 [0.01; 1.57]	0.97 [0.64; 1.46]	0.69 [0.02; 7.91]	IBR+RTX	1.42 [0.53; 3.98]	0.31 [0.10; 0.88]	1.04 [0.21; 4.06]	1.23 [0.80; 1.89]
0.47 [0.07; 2.99]	0.20 [0.01; 3.07]	1.02 [0.18; 5.69]	0.70 [0.02; 14.06]	1.05 [0.18; 6.12]	IBR+UBL	0.22 [0.05; 0.86]	0.73 [0.12; 3.75]	0.87 [0.31; 2.32]
7.26 [1.12; 202.79]	3.3 [0.08; 125.67]	15.85 [2.10; 477.99]	11.72 [0.26; 538.00]	16.44 [2.09; 495.33]	16.44 [1.10; 668.55]	IDE+RTX	3.35 [0.52; 18.65]	3.98 [1.39; 12.21]
0.24 [0.01; 9.50]	0.10 [<0.01; 6.61]	0.51 [0.01; 19.75]	0.34 [<0.01; 28.44]	0.53 [0.01; 20.76]	0.50 [0.01; 26.99]	0.03 [<0.01; 1.99]	RTX	1.18 [0.30; 5.95]
0.35 [0.15; 0.77]	0.16 [0.01; 1.21]	0.75 [0.50; 1.12]	0.53 [0.02; 6.14]	0.77 [0.43; 1.37]	0.74 [0.13; 4.32]	0.05 [<0.01; 0.37]	1.46 [0.04; 53.29]	ZAN

Model (fixed) summary for oveall hypertension: Dbar = 15.33766; pD = 15.31065; DIC = 30.64831, 15 data points, ratio 1.023, I^2 = 9%.
Model (fixed) summary for grade ≥3 hypertension: Dbar = 15.83403; pD = 15.82014; DIC = 31.65416, 15 data points, ratio 1.056, I^2 = 12%.

BLEEDING

- 7 studies (ALPINE[1], ASCEND[2], ELEVATE-RR[7], GENUINE[8], HELIOS[9-10], Huang 2018[11], RESONATE[3,12]) reporting bleeding outcomes were found as a result of the systematic search
- Acalabrutinib was associated with a lower risk of bleeding compared to ibrutinib and zanubrutinib
- The risk of grade ≥3 bleeding and major bleeding remained similar across all BTKi therapies
- Bendamustine+rituximab showed the lowest probability of bleeding (SUCRA: 0.88), while ofatumumab – the lowest probability of major bleeding (SUCRA: 0.83)

Overall bleeding (all grades)

Major bleeding (grade ≥3 bleeding)								
ACA	0.16 [0.02; 0.51]	1.35 [1.12; 1.65]	0.37 [0.05; 1.26]	N/A	0.27 [0.13; 0.49]	0.37 [0.23; 0.57]	0.15 [0.02; 0.52]	1.38 [1.06; 1.81]
1.53 [0.22; 43.90] (1.22 [0.17; 26.71])	BEND+RTX	8.58 [2.62; 57.31]	2.36 [1.73; 3.31]	N/A	1.71 [0.45; 12.01]	2.32 [0.65; 16.12]	0.97 [0.10; 9.23]	8.78 [2.64; 59.29]
0.85 [0.39; 1.82] (0.83 [0.35; 1.91])	0.54 [0.02; 4.47] (0.67 [0.03; 5.89])	IBR	0.28 [0.04; 0.95]	N/A	0.20 [0.10; 0.37]	0.27 [0.17; 0.40]	0.11 [0.02; 0.38]	1.02 [0.85; 1.23]
0.68 [0.07; 21.83] (N/A)	0.44 [0.14; 1.21] (N/A)	0.81 [0.07; 27.94] (N/A)	IBR+BEND+RTX	N/A	0.72 [0.18; 5.17]	0.98 [0.26; 6.94]	0.41 [0.04; 3.98]	3.72 [1.06; 25.51]
N/A (1.17 [0.21; 7.26])	N/A (0.92 [0.03; 14.37])	N/A (1.41 [0.32; 7.20])	N/A (N/A)	IBR+UBL	N/A	N/A	N/A	N/A
1.34 [0.32; 6.73] (1.08 [0.24; 5.54])	0.87 [0.03; 7.83] (0.89 [0.04; 7.75])	1.59 [0.31; 9.52] (1.30 [0.23; 8.09])	1.97 [0.06; 24.20] (N/A)	N/A (0.92 [0.09; 9.72])	IDE+RTX	1.35 [0.63; 3.12]	0.56 [0.07; 2.38]	5.12 [2.66; 10.92]
5.84 [1.48; 31.01] (N/A)	3.77 [0.11; 50.27] (N/A)	6.82 [2.30; 31.34] (N/A)	8.59 [0.21; 147.39] (N/A)	N/A (N/A)	4.44 [0.52; 38.55] (N/A)	OFA	0.42 [0.06; 1.52]	3.78 [2.45; 6.11]
1.66 [0.16; 52.65] (N/A)	1.04 [0.02; 57.45] (N/A)	1.92 [0.22; 58.71] (N/A)	2.40 [0.04; 155.34] (N/A)	N/A (N/A)	1.25 [0.07; 52.09] (N/A)	0.28 [0.02; 9.96] (N/A)	RTX	9.07 [2.66; 63.26]
0.99 [0.33; 2.96] (0.91 [0.28; 2.95])	0.63 [0.02; 6.19] (0.73 [0.03; 7.58])	1.17 [0.55; 2.57] (1.10 [0.49; 2.51])	1.44 [0.04; 18.77] (N/A)	N/A (0.78 [0.13; 4.30])	0.74 [0.11; 4.45] (0.84 [0.11; 5.69])	0.17 [0.03; 0.66] (N/A)	0.60 [0.02; 6.20] (N/A)	ZAN

Model (fixed) summary for oveall bleeding: Dbar = 13.18940; pD = 13.16353; DIC = 26.35293, 13 data points, ratio 1.015, I^2 = 9%.
Model (fixed) summary for grade ≥3 bleeding: : Dbar = 9.206207; pD = 9.203532; DIC = 18.409739, 9 data points, ratio 1.023, I^2 = 13%.
Model (fixed) summary for major bleeding: Dbar = 13.58686; pD = 13.58409; DIC = 27.17095, 13 data points, ratio 1.045, I^2 = 12%.

ATRIAL FIBRILLATION

- 11 studies (ALPINE[1], ASCEND[2], Burger 2019[6], ELEVATE-RR[7], GENUINE[8], HELIOS[9-10], Huang 2018[11], RESONATE[3,12], Study 116[13], Study119[14], TUGELA[15]) reporting atrial fibrillation were found
- Atrial fibrillation was more common in patients receiving ibrutinib compared to acalabrutinib and zanubrutinib
- Acalabrutinib and zanubrutinib performed better than ibrutinib+ublituximab
- Bendamustine+rituximab showed the lowest probability of bleeding (SUCRA: 0.88), while ofatumumab – the lowest probability of major bleeding (SUCRA: 0.83)

Overall atrial fibrillation (all grades)

Grade ≥3 atrial fibrillation											
ACA	0.26 [0.01; 1.48]	1.73 [1.09; 2.83]	1.11 [0.04; 8.14]	1.32 [0.51; 3.33]	18.89 [2.84; 527.53]	N/A	N/A	0.41 [0.12; 1.14]	0.05 [<0.01; 0.31]	0.45 [0.05; 2.44]	0.64 [0.30; 1.35]
0.55 [0.04; 17.42]	BEND+RTX	6.77 [1.09; 193.56]	4.28 [2.01; 10.67]	5.24 [0.69; 155.08]	87.06 [5.28; 7027.04]	N/A	N/A	1.60 [0.21; 46.92]	0.20 [<0.01; 8.26]	1.80 [0.11; 67.37]	2.51 [0.36; 73.32]
1.34 [0.57; 3.23]	2.39 [0.07; 35.39]	IBR	0.63 [0.02; 4.98]	0.76 [0.33; 1.66]	10.75 [1.74; 294.16]	N/A	N/A	0.24 [0.07; 0.72]	0.03 [<0.01; 0.17]	0.26 [0.03; 1.32]	0.37 [0.20; 0.64]
0.08 [<0.01; 3.17]	0.14 [0.02; 0.56]	0.06 [<0.01; 2.57]	IBR+BEND+RTX	1.23 [0.13; 38.24]	20.28 [1.05; 1771.36]	N/A	N/A	0.38 [0.04; 11.68]	0.05 [<0.01; 2.01]	0.42 [0.02; 16.97]	0.58 [0.07; 18.43]
1.82 [0.47; 7.49]	3.21 [0.08; 59.91]	1.35 [0.48; 4.13]	23.26 [0.47; 762.40]	IBR+RTX	14.48 [1.92; 425.23]	N/A	N/A	0.31 [0.07; 1.26]	0.04 [<0.01; 0.27]	0.34 [0.03; 2.14]	0.49 [0.18; 1.31]
0.20 [0.01; 1.75]	0.32 [<0.01; 10.53]	0.15 [0.01; 1.06]	2.31 [0.02; 124.13]	0.11 [<0.01; 1.03]	IBR+UBL	N/A	N/A	0.02 [<0.01; 0.19]	0 [<0.01; 0.04]	0.02 [<0.01; 0.30]	0.03 [<0.01; 0.23]
0.23 [<0.01; 15.96]	0.41 [0.01; 5.21]	0.17 [<0.01; 12.63]	2.97 [0.07; 68.58]	0.13 [<0.01; 10.43]	1.26 [0.01; 266.11]	IDE+BEND+RTX	N/A	N/A	N/A	N/A	N/A
11.89 [0.23; 646.2]	20.24 [0.12; 2334.54]	8.87 [0.19; 437]	148.78 [0.74; 24176.14]	6.50 [0.12; 369.59]	65.94 [0.81; 9963.07]	52.56 [0.17; 16756.50]	IDE+OFA	N/A	N/A	N/A	N/A
1.86 [0.15; 60.43]	3.37 [0.09; 133.43]	1.41 [0.10; 50.15]	24.81 [0.50; 1427.96]	1.05 [0.06; 41.88]	10.58 [0.33; 1167.72]	8.72 [0.10; 1134.22]	0.17 [<0.01; 27.73]	IDE+RTX	0.12 [<0.01; 1.11]	1.09 [0.12; 7.04]	1.55 [0.44; 6.25]
22.48 [2.93; 675.56]	42.09 [0.76; 2632.01]	16.42 [2.77; 450.81]	312.29 [4.26; 27675.26]	12.46 [1.46; 391.83]	127.20 [7.09; 11952.96]	110.36 [0.90; 21674.46]	1.91 [0.21; 56.38]	12.42 [0.22; 788.95]	OFA	9.08 [0.52; 344.41]	12.44 [1.99; 357.64]
N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	RTX	1.41 [0.25; 13.66]
2.77 [0.76; 10.89]	4.92 [0.13; 87.49]	2.06 [0.80; 5.95]	35.57 [0.72; 1122.5]	1.53 [0.35; 6.70]	13.99 [1.55; 465.61]	12.27 [0.15; 996.12]	0.24 [<0.01; 12.24]	1.48 [0.04; 26.05]	0.12 [<0.01; 1.03]	N/A	ZAN

Model (fixed) summary for oveall atrial fibrillation: Dbar = 18.79055; DIC = 37.59260, 19 data points, ratio 0.9896, I^2 = 4%.
Model (fixed) summary for grade ≥3 atrial fibrillation: : Dbar = 9.206207; pD = 9.203532; DIC = 18.409739, 9 data points, ratio 1.023, I^2 = 13%.

LEGEND

Chemoimmunotherapy · Immunotherapy (anti-CD20) · BTK inhibitor monotherapy · BTK inhibitor + immunotherapy · BTK inhibitor + chemoimmunotherapy · PI3K inhibitor + immunotherapy · PI3K inhibitor + chemoimmunotherapy

ACA – acalabrutinib; **BEND** – bendamustine; **IBR** – ibrutinib; **IDE** – idelalisib; **N/A** – results not available; **OFA** – ofatumumab; **RTX** – rituximab; **UBL** – ublituximab; **ZAN** - zanubrutinib
Comparison of the included interventions: risk ratio [95% CrI]. Each cell gives the effect of the column-defining intervention relative to the row-defining intervention.
Results colors represent direction of statistical significance [light green – column-defining intervention significantly better than row-defining intervention; light orange - column-defining intervention significantly worse than row-defining intervention].

CONCLUSIONS

The results of the NMAs suggest significant differences between BTKi therapies in relapsed/refractory CLL patients regarding hypertension, atrial fibrillation, and bleeding.

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