How relevant are the control cohorts of clinical trials in patients with newly diagnosed DLBCL in a daily praxis?

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Background.

The development of novel therapeutical strategies is essential for improvement of survival of patients (pts) with newly diagnosed (dg.) diffuse large B-cell lymphoma (DLBCL). Almost all studies trying to improve the outcome over R-CHOP have failed. The study cohort selection and its representativeness is one of the important questions which is repeatedly discussed. We have decided to compare the outcome of real-world data of R-CHOP-treated pts with control arms of two studies. First study is a negative one – GOYA trial (Vitolo, 2017) testing replacement of rituximab by obinutuzumab; and the second study is a positive one – POLARIX trial (Tilly, 2022) testing the substitution of vincristine by an antibody-drug conjugate polatuzumab vedotin. The aim of this analysis is to understand the relevance of the results of clinical trials for daily praxis.

Methods.

Characteristics and outcomes of pts in the control cohorts of the GOYA trial (*n* = 710) and POLARIX trial (*n* = 439) were compared retrospectively with cohorts of pts identified in the Czech national non-Hodgkin lymphoma registry NiHiL (NCT03199066) who fulfilled the inclusion/exclusion criteria (I/E crit.) of the respective studies and were treated in the recruitment period of each study.

Results.

Altogether 4602 pts with *de novo* DLBCL, their characteristics and information on treatment and outcomes were identified in the NiHiL registry between 2008–2020. Of them, 1572 pts were dg. between years 2011–2014 and 1182 between 2017–2019.

From the cohort of 1572 pts dg. between 2011–2014, 1028 (65%) pts received R-CHOP, and 778 (50% of all and 76% of R-CHOP cohort) pts met all main I/E crit. of the GOYA study. The pts (median age 64 years vs. 62 years in the control cohort of the GOYA trial) were dg. with advanced clinical stage (aCS) in 60% (vs. 76%; Table 1), PS ECOG 2 in 21% (vs. 14%), elevated LDH 66% (vs. 57%), and IPI 3–5 in 49% (vs. 43%). The median time from dg. to treatment initiation was 25 days for both our pts and the GOYA control arm. A total of 82% of pts completed the planned ≥ 6 cycles of R-CHOP (vs. 85%). Our pts presented with an improved ORR of 88% vs. 80% in the GOYA study (CR rate 73% vs. 34%; CT assessment), prolonged survival in terms of PFS (72% vs. 67% at 3 years, 67% vs. 63% at 5 years; Fig. A), and similar OS (80% vs. 81% at 3 years, 74% vs. 78% at 5 years), with median follow-up of 99.6 months (range 0.4–135.6).

Among the 1182 pts dg. between 2017–2019, a total of 773 (65%) pts were treated by R-CHOP, from which 465 pts (39% of all DLBCL and 60% of R-CHOP pts) met the I/E crit. of the POLARIX study. Median age was 67 years (vs. 66 years in the control cohort of the POLARIX trial) aCS was observed in

76% (vs. 88%), PS ECOG 2 in 28% (vs. 17%), elevated LDH in 79% (vs. 65%), and IPI 3–5 in 64% (vs. 62%). The median time from dg. to treatment initiation was 29 days (vs. 27 days). Majority of pts (80%) received all the planned ≥ 6 cycles of R-CHOP (vs. 86%). Our pts had slightly decreased ORR in comparison to the POLARIX control cohort (76% vs. 84%; CR rate 63% vs. 74%; PET/CT assessment). The PFS of both cohorts of pts was 70% at 2 years (Fig. B). But, the 2-year OS was inferior in the NiHiL control cohort (78% vs. 89%), with median follow-up time of 35.6 months (range 1.0–62.9).

Conclusions.

The pts with newly dg. DLBCL in the real-life setting defined by the I/E crit. of the study cohorts (GOYA, POLARIX) have similar primary endpoints outcomes as the control R-CHOP arms of those study cohorts. Thus, the study results are relevant for the daily praxis. It has to be however taken into account that I/E crit. defined cohorts represent only 76% (GOYA), and 60% (POLARIX) of all R-CHOP-treated pts in the real life.

Table 1. Baseline characteristics.

	GOYA trial				POLARIX trial			
	NiHiL control arm		Study control arm		NiHiL control arm		Study control arm	
	n	%	n	%	n	%	n	%
Recruitment period	2011–2014		2011–2014		2017–2019		2017–2019	
Dg. during recruitment	1572				1182			
Treated by R-CHOP	1028	65			773	65		
Included into analysis	**778**	76	**710**		**465**	60	**439**	
Median age (range)	64	(19–88)	62	(18–83)	67	(20–80)	66	(19–80)
Age category	778				465		439	
≤ 60 years	297	38			106	23	131	30
> 60 years	481	62			359	77	308	70
Gender	778		710		465		439	
male	393	51	382	54	238	51	234	53
Clinical stage	778		709		465		439	
I or II	313	40	171	24	110	24	52	12
III or IV	465	60	538	76	355	76	387	88
No. of extranodal sites	778		710		465		439	
0	240	31	244	34	111	24	226	52
1	299	38	466	66	149	32		
≥ 2	239	31			205	44	213	49
Bulky disease ≥ 7.5 cm	680		708		420		439	
yes	295	43	262	37	198	47	192	44
PS ECOG	778		710		465		438	
0 or 1	616	79	611	86	337	72	363	83
2	162	21	99	14	128	28	75	17
LDH level	778		706		465		438	
elevated	513	66	403	57	367	79	284	65
IPI score	778		710		465		439	
low/low-intermediate	399	51	408	58	165	35	167	38
high-intermediate	198	25	192	27	155	33	272	62
high	181	23	110	16	145	31		
Cell of origin	214		462		384		338	
GCB	126	59	269	58	198	52	168	50
non-GCB	88	41	193	42	186	48	170	50
Median time from dg. to treatment, days (IQR, range for GOYA)	25	(13–41)	25	(1–265)	29	(19–43)	27	(19–41)

Figure. Survival curves of patients from the NiHiL registry who fulfilled the inclusion/exclusion criteria of the GOYA (**A**; *n* = 778) and POLARIX (**B**; *n* = 465) trial.