Real World Population-Based Exploration of the Pathology Subtyping and Treatment-Modalities of Diffuse Large B-Cell Lymphoma in Belgium in Relation to Survival

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INTRODUCTION AND OBJECTIVES

To determine the patterns of care for DLBCL in Belgium (2013-2015)

- Emphasis on elderly patients (28% ≥ 80 years old), with comorbidities & other tumours (12%).
- Most survival data comes from clinical trials which exclude these patients.
- Other registry studies usually do not have detailed information on treatments.

Why do we want to do this?

- What is the clinical practice in Belgium for all DLBCL patients?
- How are elderly patients treated in Belgium? Are these treatments successful?

METHODS

The Belgian Cancer Registry (BCR) collects, processes and analyses data on all new cancers diagnosed in Belgian residents by independent collection of double input: oncological care programs and pathology reports. Coded data were obtained for **all adult (≥ 20 year) DLBCL diagnosed between 2013 and 2015 (n=1888).** Vital status was available until July 2019.

Data extraction:

- Pathology reports : 10 biomarkers (IHC – FISH)
- Oncological care programs : WHO performance status – Ann Arbor staging

Estimation of patterns of care (≤2 years from diagnosis)

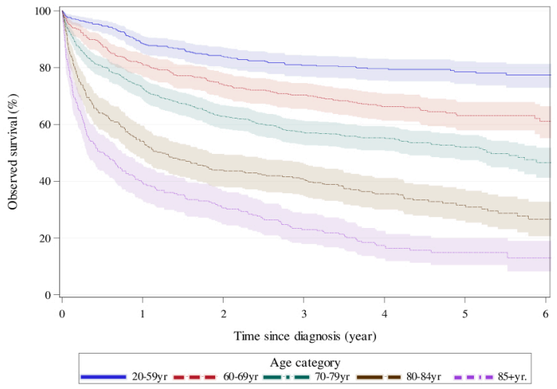
- Inference of different treatments based on health insurance data of reimbursed drugs
- Stem cell transplantation - radiotherapy - lumbar puncture based on nomenclature codes

An in-house algorithm was set up to define:

- Chemotherapy regimen (e.g. R-CHOP / R-DHAP / …)
- Number of cycles + cycle interval
- Switch from one regimen to another (i.e. 1st -> 2nd line e.g. R-CHOP -> R-DHAP)

RESULTS

2-year OS of all patients : 63.07% with a clear influence of age (30-84%).

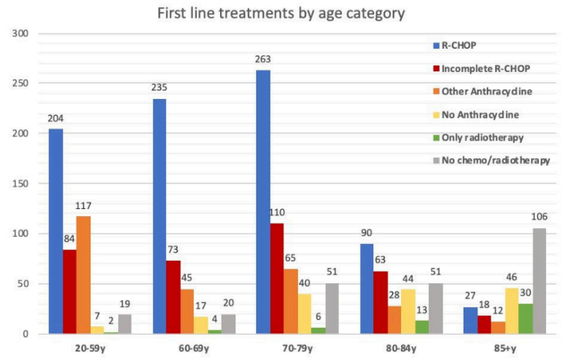


Biomarkers:

Information on cell of origin (COO) was available in 63% of cases; KI-67, BCL2, BCL2 & MYC expression in 58%, 62%, and 16% of cases, respectively; *MYC*, *BCL2* & *MYC* gene rearrangements in 11% and 9% of cases. Of the evaluable cases, 49% were double expressors (DE) and 10% were double-hit (DH) DLBCL (FISH only performed in ±10%). No major differences were observed between age groups.

RESULTS *(continued)*

First line systemic treatment was started in 85% **(n=1596)** (Rituximab-containing in 96%) decreasing with age to only 46% in very elderly patients (≥85 year). The median [IQR] delay from diagnosis to treatment was 21 [13–33] days.



Second line treatment was started in 16% **(n=253)** of those receiving first line treatment **(**7% refractory / 9% relapse, defined as before versus after 12 weeks of last administration of first line treatment). The majority was platinum based, with a 5y-OS of only 25%. Autologous transplantation (ASCT) was performed as part of first line treatment in 34/80 (42%), of second line in 43/80 (54%), and third or further lines in 3/80 (4%). The 5y-OS after ASCT was 67%, similar in 1st and 2nd line.

All cases	N (%) N=1888	20-59yr N=432 (22.8%)	60-69yr N=393 (20.8%)	70-79yr N=535 (28.3%)	80-84yr N=289 (15.3%)	85+yr N=239 (12.7%
Second Line Treatments	**N=253**	**N=83**	**N=71**	**N=71**	**N=24**	**N=4**
Platinum Based	180 (71%)	66 (80%)	56 (79%)	45 (63%)	12 (50%)	1 (25%)
Cytarabine Based[a]	8 (3%)	4 (5%)	3 (4%)	1 (1%)	0 (0%)	0 (0%)
Anthracycline Based	16 (6%)	7 (8%)	2 (3%)	6 (8%)	1 (4%)	0 (0%)
Bendamustine Based	8 (3%)	0 (0%)	0 (0%)	1 (1%)	5 (21%)	2 (50%)
Palliative	19 (8%)	1 (1%)	4 (6%)	11 (15%)	3 (13%)	0 (0%)
Other[b]	22 (9%)	5 (6%)	6 (8%)	7 (10%)	3 (13%)	1 (25%)
% of all cases (n=1888)	13%	19%	18%	13%	8%	2%
% of treated in 1st line (n=1596)	16%	20%	19%	15%	11%	4%
Refractory[c]	111 (7%)	34 (8%)	35 (9%)	33 (7%)	8 (4%)	2 (2%)
Relapsed[c]	142 (9%)	49 (12%)	36 (10%)	39 (8%)	16 (7%)	2 (2%)
HSCT[d]	**N**					
Autologous[e]	80	54	24	2	0	0
Allogeneic	6	5	1	0	0	0

a: Not containing platinum, anthracyclines nor bendamustine.
b: Includes CNS-directed therapy, only gemcitabine containing, experimental therapies.
c: Presumed refractory of relapsed when start 2nd line of therapy < or >12 weeks from last administration of first line treatment.
d: Hematopoietic stem cell transplantation, after 1st, 2nd or further lines of therapy. In 64/80 cases ASCT performed ≤2 years from diagnosis.

Limitations of this study :

- Information on some biomarkers unavailable in 10-85% of cases (FISH done in 10%).
- No information on non-reimbursed drugs (i.e. experimental drugs – clinical trials).
- Indirect deduction of the ”intended” treatments.
- Reasons for stop or change of therapy are unknown (tolerance, progression, …).
- Remission status of patients is unknown.
- Unavailability of other established prognostic markers like IPI.

RESULTS *(Multivariable analysis)*

Shown below are the adjusted hazard ratios from a multivariable analysis based on Cox Models including age category, gender, region, WHO PS, cell of origin, KI67 expression, comorbidities, other malignancies, and first line treatments. For some variables we considered a time-point interaction. This table is not exhaustive but is a selection of the most clinically relevant variables and subcategories.

Variable		Hazard ratio	Confidence interval	P Value
Age category	*60-69 year*	1.85	*1.41-2.42*	<0.0001
(Ref: 20-59 year)	*70-79 year*	2.50	*1.94-3.23*	<0.0001
	80-84 year	3.83	*2.91-5.04*	<0.0001
	85+ year	5.31	*3.99-7.06*	<0.0001
Gender	*Male*	1.23	*1.07-1.40*	0.0033
Performance status early[a]	*>1*	4.60	*3.46-6.12*	<0.0001
Performance status late[a]	*>1*	1.95	*1.57-2.41*	<0.0001
BCL2 overexpression[b]	*Present*	1.72	*1.15-2.57*	0.0280
Cell of origin[b]	*Non-GCB*	1.46	*1.12-1.91*	0.0053
Comorbidity[c]	*Respiratory*	1.47	*1.19-1.81*	0.0003
	Diabetes	1.20	*1.01-1.43*	0.0417
Other malignancies[d]	*Before (n=118)*	1.29	*1.02-1.64*	0.0345
	After (n=110)	2.42	*1.84-3.17*	<0.0001
First line treatment[e]	*Complete R-CHOP[f]*	0.38	*0.30-0.48*	<0.0001
	Other Anthracycline	0.74	*0.57-0.97*	0.0264

a: Impact on OS during time period ≤0,25 (early) versus >0,25 (late) years from incidence.
b: Impact on OS during time period >1 year from incidence. Not significant at ≤1 year.
c: Based on reimbursed drugs in same time period. Cardiovascular comorbidity was not retained because of a non-significant type III test.
d: Diagnosis of another malignancy reported before the incidence of the DLBCL in 118 cases and on the same day or later in 110 cases.
e: All treatment categories have been included in the model as time dependent variables to overcome immortal time bias but only those associated with a significant HR are shown in this table.
f: R-(mini)CHOP for ≥ 6 cycles (≥ 4 if Ann Arbor stage = 1)

CONCLUSIONS

- **In Belgium, 28% of DLBCL patients are ≥ 80 years old limiting treatment options.**
- **A significant proportion of patients did not get any treatment – increasing with age.**
- **Elderly patients were more frequently *(4-12%)* treated with radiotherapy alone.**
- **Most *(63%)* older patients *(70-84 yr-old)* received anthracyclines in first line.**
- **Those who completed the full R-(mini)CHOP course had the best prognosis *(HR 0.38).* Even up to the age of 85, confirming its use in selected very elderly patients.**
- **Second line therapy was initiated in 16% of patients *(20 to 4% decreasing with age)* and was mostly platinum based with a poor prognosis without ASCT consolidation.**
- **Age seems to be the most discriminating factor related to survival *(HR 1.9 to 5.3 for increasing age)* on top of performance status *(HR 4.6 if >1).***
- **Up to 12% have other recent malignancies and have a worse prognosis *(HR 1.3-2.4).***
- **Disease characteristics did not seem to differ between age categories.**

ACKNOWLEDGEMENTS AND CONTACT

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