Aggressive Lymphoma Workshop

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How to treat elderly patients
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Disclosures

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Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other
Takeda	X						
Servier	x						
Genmab						X	
AbbVie						X	
Celgene						X	
Y-mAbs Therapeutics			X				
Lilly					X		

DLBCL: disease of the elderly

→ 63% ≥ 65 yr
→ 33% ≥ 75 yr
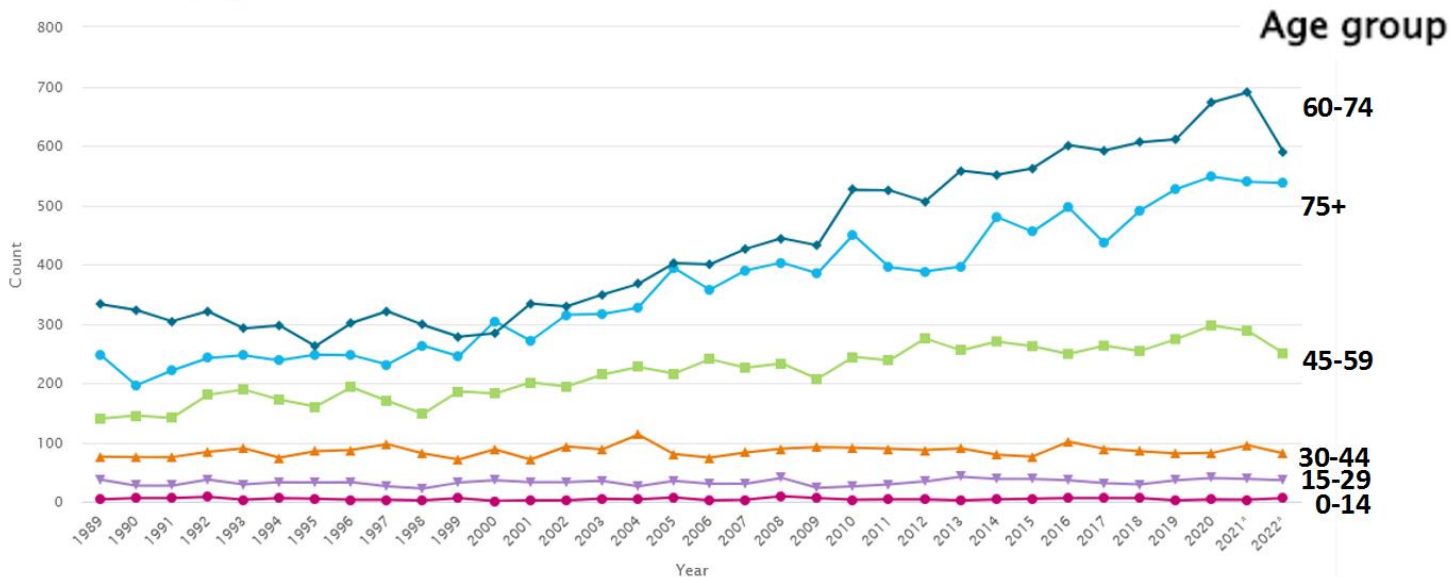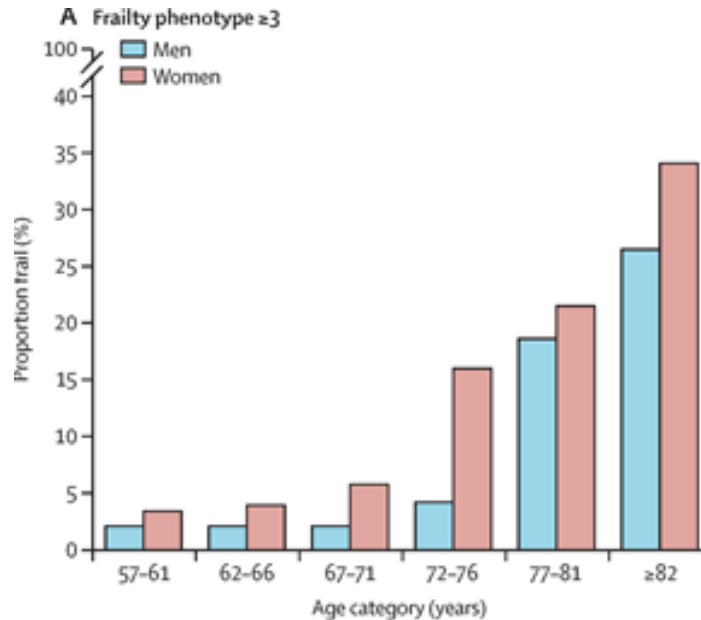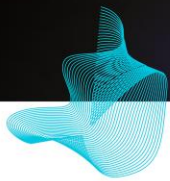

Dutch Cancer Registry 2022 (NCR)

Relative survival DLBCL population based data NL
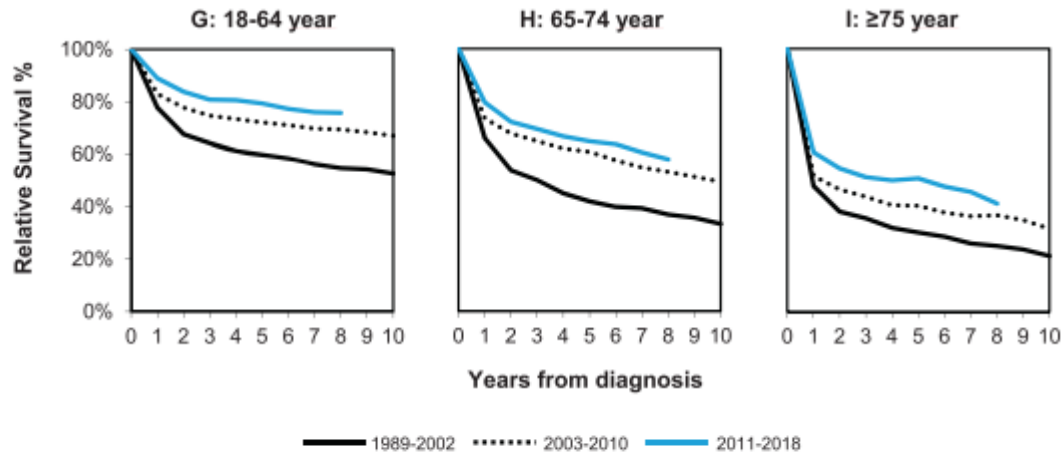
- relative survival has improved since introduction rituximab
- outcome elderly less good

Frailty prevalance

A Frailty phenotype ≥3

Higher prevalence rates frailty
- rises with age
- women
- low income
- low educational level
- ethnic minorities

75% people with frailty
have multimorbidity

Hoogendijk EO, et al. Lancet 2019

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Cardiovascular diseases most prominent

	Non-Hodgkin's lymphoma		
	< 60 years (%)	60–69 years (%)	≥ 70 years (%)
No co-morbidity	80	57	39
COPD	2	6	10
Cardiovascular	3	15	22
Cerebrovascular	1	3	6
Hypertension	6	14	14
Diabetes mellitus	1	8	10
Other malignancy	4	9	14
Other	5	9	12
(n=)	(372)	(222)	(310)

→ preclude use of standard R-CHOP

Van Spronsen DJ et al. Ann Hematol 1999

Danish population-based study DLBCL (1011 pts)

	75–79 years	80–84 years	>85 years	All
Number (%)	403 (100)	367 (100)	241 (100)	1011 (100)
Comorbidity (CCI)[a]				
None (0)	160 (40)	158 (43)	100 (41)	418 (41)
Moderate (1–2)	154 (38)	143 (39)	94 (39)	391 (39)
High (3-)	89 (22)	66 (18)	47 (20)	202 (20)
Treatment				
Standard	336 (83)	239 (65)	76 (32)	651 (64)
Less intensive	36 (9)	62 (17)	45 (19)	143 (14)
Palliative	31 (8)	66 (18)	120 (50)	217 (21)

Juul MB, et al. Eur J Cancer 2018

Aging is a heterogeneous phenomenon

same-age individuals markedly differ
in physiological or psychosocial robustness

92 yr

Age-associated conditions contribute

- to reducing access to therapeutic options
- to increasing treatment side effects
- choice of treatment?

        →   - older patients underrepresented in clinical trials

           - therapy decision: subjective assessment treating physician

Assessment fitness

- performance status does not accurately predict treatment related complications
- no uniform consensus optimal tool
- comprehensive geriatric assessments
  - time consuming
  - consultation geriatrician
  - not validated to guide treatment
- unrealistic many patients aggressive lymphomas

FIL: Simplified Geriatric Assessment and Age (< 80 or ≥ 80 yrs)

1 point for ability to:

ADL
bathing
dressing
toileting
transferring
feeding
continence

IADL
use phone
shop
prepare food
keep house
do laundry
travel public
handle money
take own medication

CIRS-G
Comorbidity Index Rating Scale-for Geriatrics
comorbidity 14 organ systems
each rated from 0-5
0 = no impairment
5 = life threatening impairment

Merli F, et al. J Clin Oncol 2021

Criteria for simplified Geriatric Assessment

Criteria	Fit (54%)	Unfit (28%)		Frail (18%)
ADL	≥ 5[a]	< 5[a]	6[a]	< 6[a]
IADL	≥ 6[a]	< 6[a]	8[a]	< 8[a]
CIRS-G	0 score = 3-4, ≤ 8 score = 2	≥ 1 score = 3-4, > 8 score = 2	0 score = 3-4, < 5 score = 2	≥ 1 score = 3-4, ≥ 5 score = 2
Age	< 80	< 80	≥ 80	≥ 80

n= 1207
median age 76 yr (65-94)

Merli F, et al. J Clin Oncol 2021

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Overall survival by simplified Geriatric Assessment
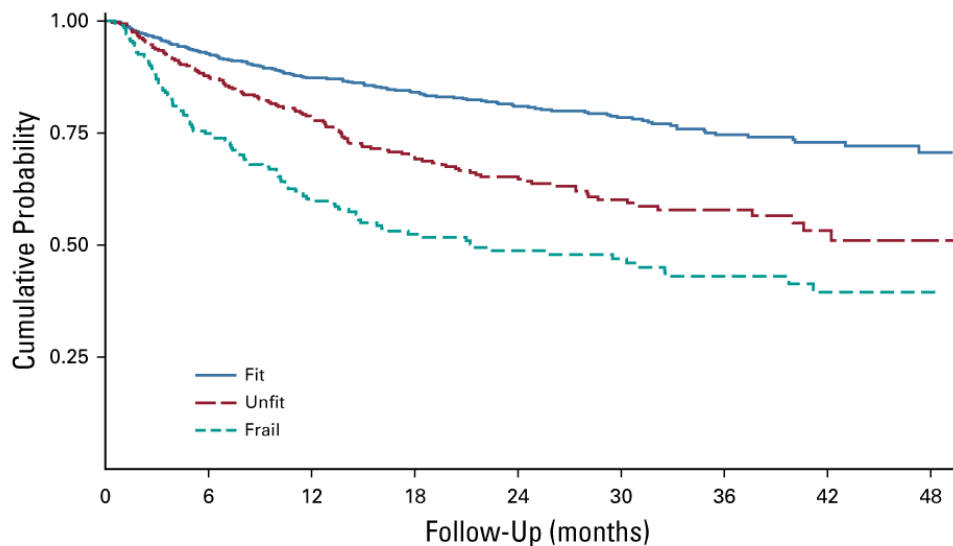
Merli F, et al. J Clin Oncol 2021

Elderly Prognostic Index: sGA + IPI+ Hb

(B) EPI model	n (%)	3-Year OS (95% CI)	HR (95% CI)	P
Risk groups (score)	1,065	66 (62 to 69)	—	—
Low (0-1)	250 (23)	87 (81 to 91)	1.00	—
Intermediate (2-5)	510 (48)	69 (63 to 73)	2.57 (1.72 to 3.84)	< .001
High (6-8)	305 (29)	42 (36 to 49)	6.21 (4.17 to 9.25)	< .001
High v intermediate	—	—	2.41 (1.91 to 3.05)	< .001

Merli F, et al. J Clin Oncol 2021
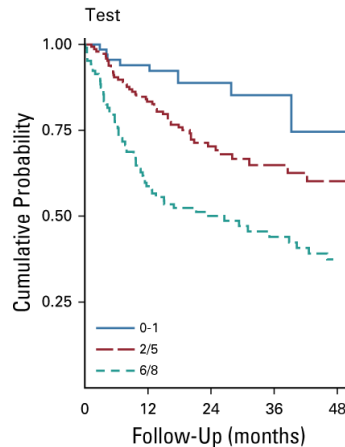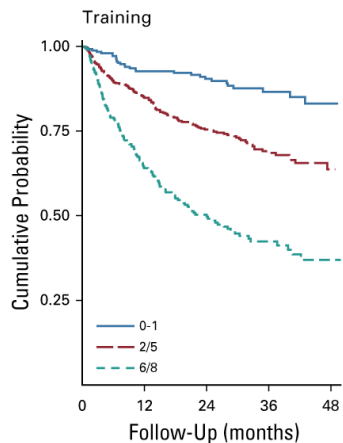
Gait speed

walk for 4 meters and record speed in meters per second (m/s) with stopwatch
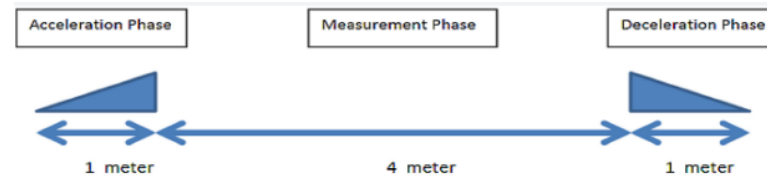
predicts outcomes independent of performance status among older patients with blood cancers

Table 3. Survival estimates by gait speed categories

Gait, m/s	Deaths (per 100 person-years)	Median OS (mo)	1-y OS (%)*	2-y OS (%)*	Log-rank test
≥0.80	12.85	NA (>35)	85.7 ± 5.6	79.3 ± 7.4	<.0001
0.60-0.80	19.77	NA (>35)	83.0 ± 6.3	66.9 ± 9.8	
0.40-0.60	33.20	24.9	71.2 ± 12.3	54.8 ± 16.4	
<0.40	84.86	11.8	47.0 ± 18.7	26.4 ± 21.1	

Liu MA, et al. Blood 2019

Randomized study: geriatric consultation vs SOC

- lymphoma, leukemia, m myeloma
- ≥ 75 yr, pre-frail or frail
- n = 160
- primary endpoint: 1 yr OS

✓ no difference OS
✓ no reduction
   - emergency department visits
   - hospital admissions
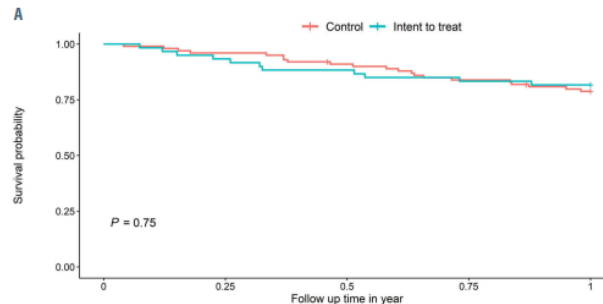   - days in hospital
✓ useful management several geriatric domains

$P = 0.75$

Table 3. Survey results of oncologists' opinions regarding value of geriatric consultation.[a]

Domains of care	Number of responses	% who answered 4 or 5 (95% CI)
Evaluating cognition	35	85.7 (69.7 - 95.2)
Connecting patients to resources	35	80.0 (63.1 - 91.6)
Diagnosing frailty	35	77.1 (59.9 - 89.6)
Managing non-oncologic comorbidities	35	77.1 (59.9 - 89.6)
Tailoring end-of-life care	35	71.4 (53.7 - 85.4)
Informing treatment decisions	35	62.9 (44.9 - 78.5)

[a]For each question, responses were rated on a Likert scale ranging from 0 = not at all useful to 5 = very useful. CI: confidence interval.

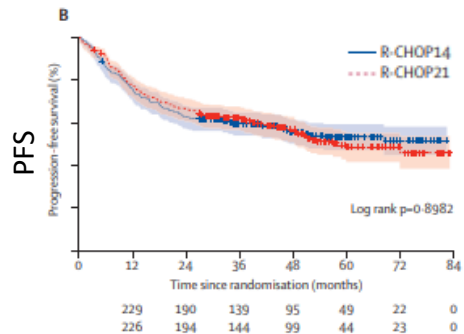DuMontier C, et al. Haematologica 2022

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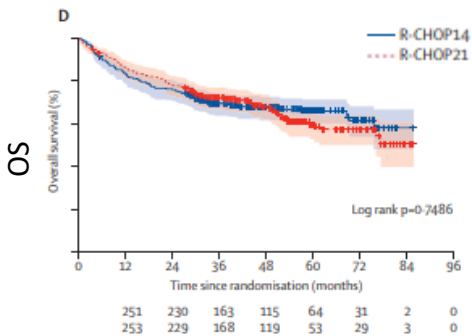# Fit patients: anthracycline-based therapy → R-CHOP-21

DLBCL, 60-80 yrs
Efficacy and safety:
8 cycles R-CHOP-21 = 8 cycles R-CHOP-14

R-CHOP-21
3-yr PFS   62%
5-yr PFS   49%

R-CHOP-21
3-yr OS   72%
5-yr OS   60%

median follow-up 56 months

R-CHOP-21 (70% cycles G-CSF)

≥ grade 3 adverse events	
neutropenia	65%
thrombocytopenia	19%
febrile neutropenia	18%
infection + neutropenia	13%
infection - neutropenia	4%
therapy related mortality	5%

Delarue R, et al. Lancet Oncol 2013

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Fit patients: anthracycline-based therapy

systematic review elderly DLBCL and role anthracycline-based chemotherapy

Retrospective studies

Reference	No. of patients	Institution/ location	Age (y)	% of patients	IPI	3-Year OS (%)	
						Anthracycline-containing regimen	Anthracycline-free regimen
20	207	MDACC	≥80	54	≥3	63	25
21	141	Mexico	≥65	61	≥3	63	52
22	72	Emory University	≥65	25	≥4	59	38
23	128	Switzerland	≥60	49	≥3	—	—
24	378	Portugal	≥60	55	≥3	—	—
25	103	Netherlands	≥75	35	≥2*	—	—
26	73	OHSU	≥75	49	≥3	68	54
27	154	MGH	≥75	—		—	—
28	476	VA system	≥80	49	≥2*	28.1 mo (median)	13.1 mo (median)

support association between use
anthracycline-containing regimens
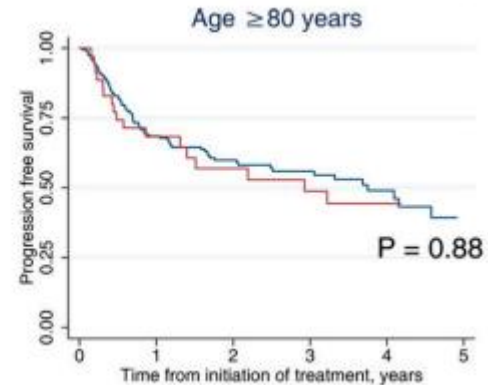and improved OS
3 yr OS 63% vs 44%

Lin RJ, et al. Blood 2017

Dose intensity matters < 80 yrs: optimal dose?

Eyre TA, et al. J Intern Med 2019
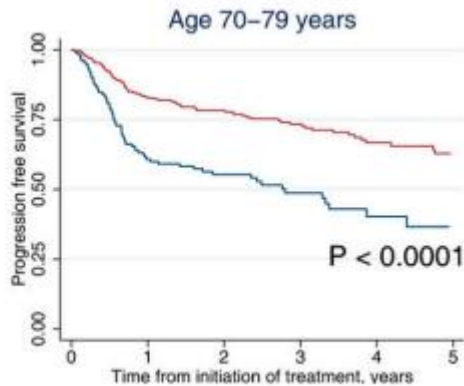
R-miniCHOP in patients > 80 yr (6 cycles)

Drug	Dose	Day
rituximab	375 mg/m^2	1
cyclophosphamide	400 mg/m^2	1
doxorubicin	25 mg/m^2	1
vincristin	1 mg	1
prednison	40 mg/m^2	1-5

outcome	
CR/CRu	63%
2-yr PFS	47%
2-yr OS	59%
TRM	8%

toxicity	≥ grade 3
neutropenia	40%
thrombocytopenia	7%
febrile neutropenia	7%

1st cycle! (TRM; haem tox; infections)
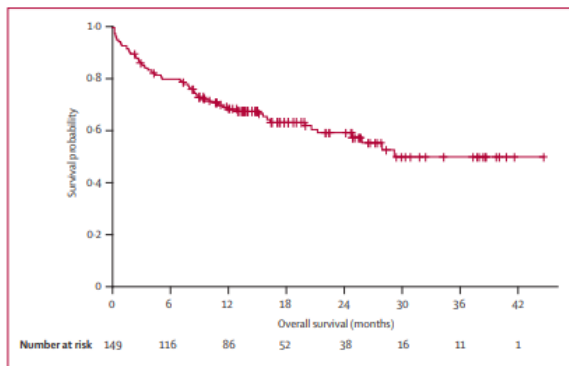
Figure 2: Overall survival

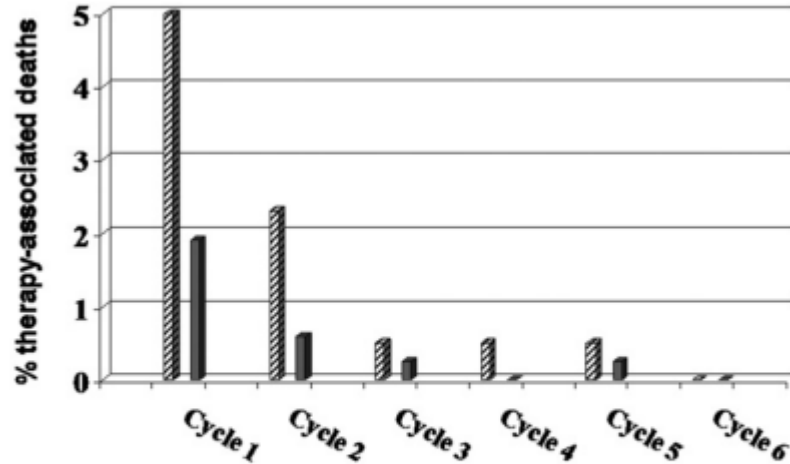Peyrade F, et al. Lancet Haematol 2017

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Prephase

Figure 1. Therapy-associated deaths in the NHL-B2 trial of CHOP in DLBCL before and after the introduction of prephase treatment. Before (▨) and after (▢) the introduction of prephase treatment.
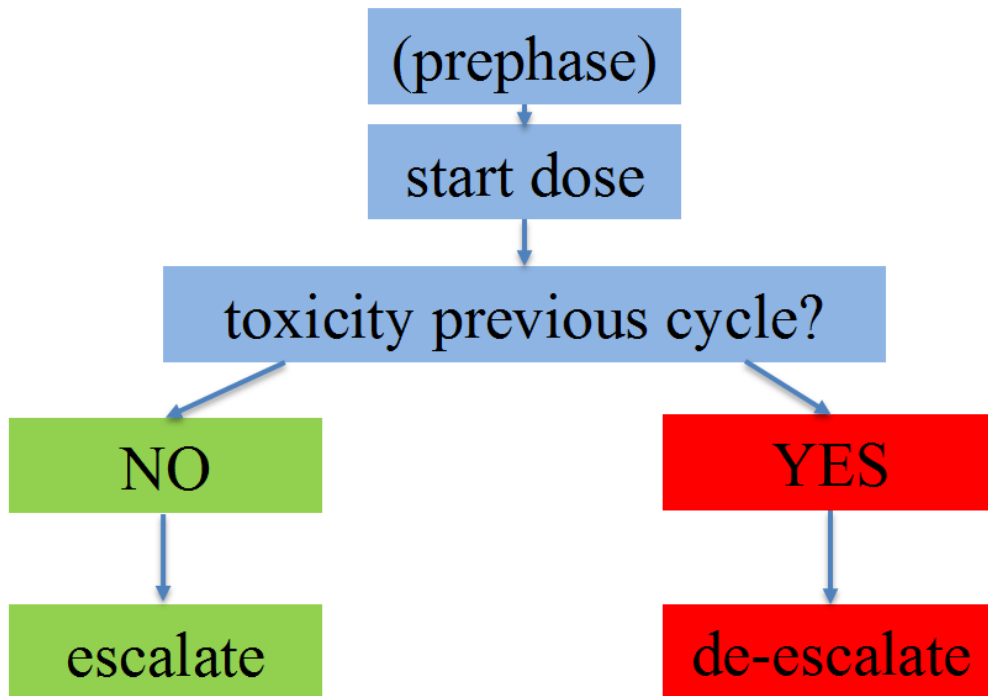
prednisone 5-7 days
60-100 mg/day

↑ performance

mania
psychosis
hyperglycemia

Pfreundschuh M, et al. J Clin Oncol 2004; 22 (14 suppl):6500

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Dynamic dosing strategy cyclophosphamide/doxorubicin

Supportive care

- more frequent follow-up

  - first cycles

  - blood counts

  - need for hydration/calorie supplementation

  - DM, glucose control

- G-CSF primary prophylaxis ≥ 65 yr

- immediate treatment infections

- fatigue after stop prednisone

  - hydrocortisone 20 mg morning/10 mg afternoon

  - prednisone tapering (50 mg on D5; 25 mg on D6; 12.5 mg on D7 + D8)

- preemptive use laxatives (chronic constipation)

- Vit D if Vit D deficient

Unfit patients

When anthracyclines are contraindicated or unfit patients
- replace doxorubicin with etoposide or gemcitabine
  R-CEOP or R-GCVP
- R-GemOx
- R-Bendamustine

Frontline treatment unfit DLBCL patients

Reference	Treatment	Age (years) median, range	Patient number	PFS	OS
Moccia et al[63]	6-8 R-CEOP21	73 (34-93)	70	53% (5 y)	47% (5 y)
	6-8 R-CHOP21	73 (21-92)	140 matched control	69% (5 y)	65% (5 y)
Shen et al[65]	6 R-GemOx	60-69	14	71% (3 y)	78% (3 y)
		≥ 70	46	42% (3 y)	61% (3 y)
Fields et al[66]	6 R-GCVP	76 (52-90)	27 (LVEF $\leq$ 50%)	55% (2y)	66% (2y)
			35 LVEF borderline + comorbidities	45% (2y)	46% (2y)
Storti et al[67]	4-6 R-Benda + 2 R	81 (71-89)	45	38% (2y)	51% (2y)

Lugtenburg PJ and Mutsaers P. Blood 2023 in press

Conclusions treatment elderly DLBCL

- geriatric assessment can be helpful: curative intent treatment?
- prephase steroids → decide curative treatment
- R-CHOP standard for fit patients
- R-miniCHOP for ≥ 80 years
- unfit or ci-anthracyclines: R-CEOP or R-GCVP
- supportive care is crucial (G-CSF…)
- unmet need for non-cytotoxic therapies
  - bispecific antibodies?
  - antibody drug conjugates?
  - monoclonal antibodies?

trials!

Thank you!

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