R-CHOP 14 - Rituximab 375 / Cyclophosphamide 750 / Doxorubicin 50 / Vincristine 2 / Prednisolone 100, diffuse large B-non-Hodgkin Lymphoma, cycle 1-6

Protocol-ID: 112 V1.1 (Complete), R-CHOP 14 (RITU375/CYCL750/DOXO50/VNCR2/PRED100), DLBCL, C1-6

Indication(s)

- NHL, B-Cell Type, Diffuse Large Cell; ICD-10 C83.3
- NHL, B-Cell Type, Follicular grade IIIb; ICD-10 C82.-, C82.7, C82.9

Protocol classification

- Classification: current standard
- Intensity: Standard dose
- Therapy mode: First line
- Therapy intention: curative

Cycles

Cycle length 14 days, recommended cycles: 6

Protocol sequences

- R-CHOP 14 (RITU375/CYCL750/DOXO50/VNCR2/PRED100), DLBCL, C1-6 (PID112) -|- RITU375, C7-8 (PID1448)

Risks

- Emetogenicity (MASCC/ESMO): moderate (30-90%)
- Neutropenia: very high (>41%)
- Febrile Neutropenia: high (>20%)
- Anemia Hb below 8g/dl: high (16-30%)
- Neuropathy: CTC AE °3-4: 7%

Therapy

Hydration: Balanced Crystalloid Solution **HYD**

Access: peripheral venous

Hydration before, during, or after antitumor therapy

Day	Substance	Dosage	Solution	Appl.	Inf. time	Procedure
1	**Balanced Crystalloid Solution**	500 ml		i.v.	60 min	60 min before Rituximab (d1)

Allergy prophylaxis: Rituximab Allergy prophylaxis (paracetamol, dimetindene) **AP**

Access: peripheral venous

Day	Substance	Dosage	Solution	Appl.	Inf. time	Procedure
1	**Paracetamol**	1000 mg		p.o.		60 min before Rituximab (d1)
1	**Dimetinden**	4 mg	NaCl 0.9% 50 ml	i.v.	5 min	30 min before Rituximab (d1)

Antiemesis: Emetogenicity moderate, GRAN i.v., without DEXA d1-3 **AE**

Access: peripheral venous

ASCO 2015, DGHO 2016, DKG 2016, MASCC/ESMO 2016, if palonosetron not available

Day	Substance	Dosage	Solution	Appl.	Inf. time	Procedure
1	**Granisetron**	1 mg	NaCl 0.9% 50 ml	i.v.	5 min	15 min before Rituximab (d1)

or other 5-HT3 receptor antagonist.

Supportive therapy: Mesna i.v., hour 0 (pre), p.o. 2 h, 6 h after onset Cyclophosphamide **SUP**

Access: peripheral venous

Mesna 0h,2h,6h, prophylaxis of urinary tract toxicity by cyclophosphamide. At the time of oxazaphosphorin injection, 20% of the oxazaphosphorin dose is injected simultaneously as mesna. 2 and 6 h after onset, oral intake of 40% of the oxazaphosporin dose.

Day	Substance	Dosage	Solution	Appl.	Inf. time	Procedure
1	**Mesna**	150 mg/m² BSA		i.v.	1 min	1 min before Cyclophosphamide (d1)
1	**Mesna**	300 mg/m² BSA		p.o.		60 min after Cyclophosphamide (d1)
1	**Mesna**	300 mg/m² BSA		p.o.		5 h after Cyclophosphamide (d1)

Medical tumor therapy: R-CHOP (RITU + CHOP d1) **CTX**

Access: central venous

R-CHOP, all substances at d1

Day	Substance	Dosage	Solution	Appl.	Inf. time	Procedure
1-5	**Prednisolone**	100 mg		p.o.		1-0-0-0
Administer at least 60 minutes before rituximab on Day 1.						
1	**Rituximab**	375 mg/m² BSA	NaCl 0.9% 500 ml	i.v.	4 h	Sequence
Init. Infusion rate 50mg/h; it can be increased by 50mg/h every 30min to max. 400mg/h. Further infusions: init. Infusion speed 100mg/h, which can be increased by 100mg/h every 30min to max. 400mg/h.						
1	**Cyclophosphamide**	750 mg/m² BSA	NaCl 0.9% 500 ml	i.v.	60 min	Sequence
1	**Doxorubicin**	50 mg/m² BSA	Dextrose 5% 250 ml	i.v.	15 min	Sequence
1	**Vincristine**	2 mg	NaCl 0.9% 50 ml	i.v.	3 min	Sequence

Hydration: Hydration after Vincristine **HYD**

Access: peripheral venous

For the prevention of vein irritation.

Day	Substance	Dosage	Solution	Appl.	Inf. time	Procedure
1	**Balanced Crystalloid Solution**	250 ml		i.v.	15 min	0 min after Vincristine

Hematopoietic growth factors: FN risk above 20%, G-CSF long-acting, pegylated **HW**

Access: - none -

Risk of febrile neutropenia (FN) >20%, ASCO 2015, DKG 2016

Day	Substance	Dosage	Solution	Appl.	Inf. time	Procedure
2	**Pegfilgrastim**	6 mg		subc	Bolus	24 h after Vincristine

Infection prophylaxis: Infection prophylaxis oral, lymphatic neoplasms **IP**

Access: - none -

Infection prophylaxis for continuous (weekly) administration until the end of therapy

Day	Substance	Dosage	Solution	Appl.	Inf. time	Procedure
1,3,5,8,10,12	**Cotrimoxazole**	960 mg		p.o.		1-0-0-0
continuous administration 3 times a week, continuing until d14 of the last cycle						
1-14	**Amphotericin B**	100 mg		p.o.		1-1-1-1
1 pipette of 1 ml (100mg), continue continuous administration until d14 of the last cycle.						

Concomitant therapy supplements

In contrast to the primary literature, prednisolone is used instead of prednisone because of more favorable pharmacokinetics at the same potency.
Dexamethasone for antiemesis on days 1-4 and prednisolone of allergy prophylaxis is covered by prednisolone of antitumor therapy.
The combination of an anthracycline and cyclophosphamide may be highly emetogenic in individual patients and require the addition of a neurokinin receptor antagonist. In this case, attention must be paid to the increase in plasma concentration of prednisolone and this may need to be adjusted.
Observe tumor lysis syndrome risk classification according to Cairo 2010; for LDH elevation without tumor bulk, use protocol "Tumor lysis syndrome prophylaxis, intermediate risk". In case of LDH elevation above twice the upper limit and tumor-bulk protocol use "tumor lysis syndrome prophylaxis, high risk".

Warnings

Doxorubicin: increased risk of cardiomyopathy, maximum cumulative dose 450-550 mg/m² KOF. In mediastinal irradiation, arterial hypertension for more than 5 years, age over 70 years or previous cardiac damage, maximum 400 mg/m².
For DOXO extravasation: dry cold (not just before or after Dexrazoxane infusion) on day of extravasation. Dexrazoxane i.v. for 3 days: 2 days 1000 mg/m², 3rd day 500 mg/m², do not use in parallel with DMSO. First infusion as soon as possible and within the first 6 hours.

Notes

Following combined chemo-immunotherapy, 2 additional cycles of rituximab mono are administered 14 days apart (RITU single dose).

Cycle diagram

Hydration: Balanced Crystalloid Solution

	Week 1 / d							Week 2 / d						
Substance	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**
Balanced Crystalloid Solution (i.v.)														

Allergy prophylaxis: Rituximab Allergy prophylaxis (paracetamol, dimetindene)

	Week 1 / d							Week 2 / d						
Substance	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**
Paracetamol (p.o.)														
Dimetinden (i.v.)														

Antiemesis: Emetogenicity moderate, GRAN i.v., without DEXA d1-3

	Week 1 / d							Week 2 / d						
Substance	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**
Granisetron (i.v.)														

Supportive therapy: Mesna i.v., hour 0 (pre), p.o. 2 h, 6 h after onset Cyclophosphamide

	Week 1 / d							Week 2 / d						
Substance	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**
Mesna (i.v.)														
Mesna (p.o.)														
Mesna (p.o.)														

Medical tumor therapy: R-CHOP (RITU + CHOP d1)

	Week 1 / d							Week 2 / d						
Substance	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**
Prednisolone (p.o.)	■	■	■	■	■									
Rituximab (i.v.)	■													
Cyclophosphamide (i.v.)	■													
Doxorubicin (i.v.)	■													
Vincristine (i.v.)	■													

Hydration: Hydration after Vincristine

	Week 1 / d							Week 2 / d						
Substance	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**
Balanced Crystalloid Solution (i.v.)	■													

Hematopoietic growth factors: FN risk above 20%, G-CSF long-acting, pegylated

	Week 1 / d							Week 2 / d						
Substance	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**
Pegfilgrastim (subc)		■												

Infection prophylaxis: Infection prophylaxis oral, lymphatic neoplasms

	Week 1 / d							Week 2 / d						
Substance	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**
Cotrimoxazole (p.o.)	■		■		■			■		■		■		
Amphotericin B (p.o.)	■	■	■	■	■	■	■	■	■	■	■	■	■	■

Cycles

Cycle length 14 days, recommended cycles: 6

Controls:

- Blood count: on day 1 and subsequently weekly
- Day -1: Echocardiography, ECG, chest X-ray Cardiotoxicity of doxorubicin, review of cardiac function before/under therapy recommended.
- Day -1: Hepatitis B (HBV) Test: HBsAg and anti-HBc Rituximab: Hep-B reactivation possible. If Hep-B serology is positive, initiate measures to prevent hepatitis B reactivation.
- Day -1: IgG Rituximab: Risk of Infection: It is recommended that immunoglobulin levels be determined prior to initiating treatment with rituximab.
- Day 1: GOT, GPT, GGT, Bilirubin, AP, Cholinesterase Doxorubicin: continuous liver monitoring is necessary during therapy. In case of elevated bilirubin, dose adjustment may be necessary. Cyclophosphamide: dose reduction may be necessary if liver function is impaired. Vincristine: dose reduction recommended in patients with impaired liver function.
- Day 1: Creatinine, glomerular filtration rate (GFR) Doxorubicin: Dose reduction necessary in patients with renal impairment. Cyclophosphamide: Dose reduction is usually recommended in the presence of impaired renal function.
- Day 1: Urine status Urinary sediment must be checked regularly for erythrocytes and other signs of uro/nephrotoxicity.
- Day 1: Na^+, K^+, Ca^{2+}, Mg^{2+} Cyclophosphamide: exclusion of electrolyte disturbances before use.

Pharmacokinetics

Doxorubicin: hauptsächlich hepatobiliäre Elimination

Original indication

Aggressive B-NHL, 61-80 years, first-line, ECOG 0-2.

Original author

Pfreundschuh M (2006)

Origin

German High-Grade Non-Hodgkin Lymphoma Study Group (DSHNHL), RICOVER-60

References

- Pfreundschuh M, Six versus eight cycles of bi-weekly CHOP-14 with or without rituximab in elderly patients with aggressive CD20+ B-cell lymphomas: a randomised controlled trial (RICOVER-60)., Lancet Oncol 2008 Feb;9(2):105-16 [PMID]
- Brusamolino E, Dose-dense R-CHOP-14 supported by pegfilgrastim in patients with diffuse large B-cell lymphoma: a phase II study of feasibility and toxicity., Haematologica 2006 Apr;91(4):496-502 [PMID]
- Cunningham D, Rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisolone in patients with newly diagnosed diffuse large B-cell non-Hodgkin lymphoma: a phase 3 comparison of dose intensification with 14-day versus 21-day cycles., Lancet 2013 May 25;381(9880):1817-26 [PMID]

Recommendations

- 10/2015: European Society for Medical Oncology
- 05/2021: National Comprehensive Cancer Network

Status

Valid since 2015-01-19, Version 1.1, last updated 2021-06-04

Last modification: V1.1: Cato check successful. Vincristine is applied as a short infusion over 3 minutes according to the recommended course of action. V1.0: Run times according to the respective summary of product characteristics. In the study, a Pre-phase therapy was initially performed in each patient, this is shown in the protocol Pre-phase, aggr. B-NHL. After the 6 cycles, 2 additional administrations of rituximab were to be given, each 2 weeks apart; the RITU1400 single administration s.c. or RITU375 single administration protocol can be used for this purpose. Only patients older than 60 years were recruited.

Important notice