Epirubicin 90 / Cyclophosphamide 600, Breast Cancer, adjuvant

Protocol-ID: 579 V1.1 (Complete), EC (EPIR90/CYCL600), Breast Ca, adj.

Indication(s)

- Breast Cancer; ICD-10 C50.-

Protocol classification

- Classification: alternative
- Intensity: Standard dose
- Therapy phase:
- Therapy intention: curative

Cycles

Cycle length 21 days, recommended cycles: 4

Protocol sequences

- EC (EPIR90/CYCL600), Breast Ca, adj. (PID579) -|- PACL80, Breast Ca, adj. (PID581)
- Neoadjuvant WSG-TP-II (Paclitaxel)
- Neoadjuvant WSG-TP-II (Letrozole)
- Neoadjuvant WSG-TP-II (Tamoxifen) -|- PERT840/TRAS8/TMXF20, Breast Ca, adj., C1 (PID2450)
- EC (EPIR90/CYCL600), Breast Ca, adj. (PID579) -|- DOCE100, adj. (PID395)

Risks

- Emetogenicity (MASCC/ESMO): moderate (30-90%)
- Neutropenia: very high (>41%)
- Febrile Neutropenia: intermediate (10-20%)
- Thrombocytopenia below 50 000/µl: low (<10%)
- Anemia Hb below 8g/dl: low (<5%)
- Dyspnea: CTC AE °3-4: 5%

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.	30 min	30 min before Epirubicin (d1)

Antiemesis: Emetogenicity high (AC), FOSAP, GRAN i.v., DEXA i.v **AE**

Access: peripheral venous

DGHO 2016, DKG 2016, MASCC/ESMO 2016, on combinations of anthracycline and cyclophosphamide

Day	Substance	Dosage	Solution	Appl.	Inf. time	Procedure
1	**Fosaprepitant**	150 mg	NaCl 0.9% 150 ml	i.v.	20 min	30 min before Epirubicin (d1)
1	**Dexamethasone**	12 mg	NaCl 0.9% 50 ml	i.v.	5 min	30 min before Epirubicin (d1)
1	**Granisetron**	1 mg	NaCl 0.9% 50 ml	i.v.	5 min	15 min before Epirubicin (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**	120 mg/m² BSA		i.v.	1 min	1 min before Cyclophosphamide (d1)
1	**Mesna**	240 mg/m² BSA		p.o.		90 min after Cyclophosphamide (d1)
1	**Mesna**	240 mg/m² BSA		p.o.		5 h after Cyclophosphamide (d1)

It is to be taken 6 hours after the start of the cyclophosphamide infusion.

Antineoplastic therapy: EPIR/CYCL Breast Carcinoma (EC) **CTX**

Access: central venous, port

Day	Substance	Dosage	Solution	Appl.	Inf. time	Procedure
1	**Epirubicin**	90 mg/m² BSA	Dextrose 5% 500 ml	i.v.	45 min	Sequence
1	**Cyclophosphamide**	600 mg/m² BSA	NaCl 0.9% 500 ml	i.v.	30 min	Sequence

Hematopoietic growth factors: FN risk 10-20%, G-CSF long-acting, pegylated **HW**

Access: - none -

Risk of febrile neutropenia (FN) 10-20% and 1 risk factor: age > 65 y, laboratory parameters (anemia, lymphocytopenia < 700/µl, hypalbuminemia, hyperbilirubinemia) previous chemotherapy, comorbidities, low performance status, advanced symptomatic tumor disease (DKG 2016)

Day	Substance	Dosage	Solution	Appl.	Inf. time	Procedure
2	**Pegfilgrastim**	6 mg		subc	Bolus	24 h after Cyclophosphamide (d1)

Use at risk: FN 10-20% and 1 risk factor, other long-acting G-CSF possible.

Warnings

Epirubicin: cardiac toxicity, maximum cumulative dose 900-1000 mg/m² KOF.
For EPIR 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

This protocol was established based on a recommendation from the AGO to extrapolate from AC + paclitaxel to EC + paclitaxel and use in dose equivalent because of the more favorable side effect profile. In the work of Smith and Khasraw, the lower cardiotoxicity of EPIR vs DOXO is addressed.
The side effect profile was based on the publication by Minckwitz for EC followed by docetaxel.

Cycle diagram

Hydration: Balanced Crystalloid Solution

	Week 1 / d						
Substance	**1**	**2**	**3**	**4**	**5**	**6**	**7**
Balanced Crystalloid Solution (i.v.)							

Antiemesis: Emetogenicity high (AC), FOSAP, GRAN i.v., DEXA i.v

	Week 1 / d						
Substance	**1**	**2**	**3**	**4**	**5**	**6**	**7**
Fosaprepitant (i.v.)							
Dexamethasone (i.v.)							
Granisetron (i.v.)							

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

	Week 1 / d						
Substance	**1**	**2**	**3**	**4**	**5**	**6**	**7**
Mesna (i.v.)							
Mesna (p.o.)							
Mesna (p.o.)							

Antineoplastic therapy: EPIR/CYCL Breast Carcinoma (EC)

	Week 1 / d						
Substance	**1**	**2**	**3**	**4**	**5**	**6**	**7**
Epirubicin (i.v.)							
Cyclophosphamide (i.v.)							

Hematopoietic growth factors: FN risk 10-20%, G-CSF long-acting, pegylated

	Week 1 / d						
Substance	**1**	**2**	**3**	**4**	**5**	**6**	**7**
Pegfilgrastim (subc)							

Cycles

Cycle length 21 days, recommended cycles: 4

Controls:

- Blood count: on day 1 and subsequently weekly
- ECG Cardiotoxicity of epirubicin, check cardiac function before/under therapy recommended. See technical info
- Day 1: GOT, GPT, GGT, Bilirubin, AP, Cholinesterase Epirubicin: continuous liver monitoring is necessary during therapy. In case of elevated bilirubin, dose adjustment, if necessary, see summary of product characteristics. Cyclophosphamide: dose reduction is recommended in case of impaired liver function.
- Day 1: Creatinine, glomerular filtration rate (GFR) Epirubicin: If serum creatinine levels are elevated (> 5 mg/dl), the dose should be reduced. Cyclophosphamide: In case of impaired renal function, dose reduction is recommended.
- 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

Epirubicin: hepatischer Abbau, 50% biliäre Elimination
Cyclophosphamid: hepatischer Abbau, hauptsächlich renale Elimination

Original indication

Paclitaxel weekly, Breast Cancer, adjuvant

Original author

Sparano JA (2008)

Origin

The Eastern Cooperative Oncology Group, Southwest Oncology Group, Cancer and Leukemia Group, Noth Central Cancer

Treatment Group

References

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- von Minckwitz G, Capecitabine in addition to anthracycline- and taxane-based neoadjuvant treatment in patients with primary breast cancer: phase III GeparQuattro study. J Clin Oncol 2010 Apr 20;28(12):2015-23. doi: 10.1200/JCO.2009.23.8303. PMID: 20308671. [PMID]
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Recommendations

- 12/2023: European Society for Medical Oncology

Status

Valid since 2023-09-18, Version 1.1, last updated 2023-09-09

Last modification: V1.1: Protocol name changed according to current standard V1.0: Cato test successful. Use this scheme for first 4 cycles, then use protocol EC x 4 followed by PACL, Breast Ca, adj., B. V0.1: Cyclophosphamide duration and sequence according to primary literature. Epirubicin duration is according to carrier solution volume.

Important notice