Adjuvant chemotherapy with or without darbepoetin alpha in node-positive breast cancer: survival and quality of life analysis from the prospective randomized WSG ARA trial

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Background

Modern adjuvant chemotherapy of early breast cancer (BC) may cause considerable chemotherapy-associated anemia (CAA). Darbepoetin alpha (DA) is currently used to reduce CAA rates. The effect of erythropoiesis stimulating factors on BC survival is still a controversial issue [1-4]. The WSG ARA trial evaluates the effect of supportive use of DA in node positive BC patients treated with chemotherapy on survival.

Endpoints

Primary endpoint: event-free survival (EFS: relapses, death without disease evidence, 2nd malignancy)

Secondary endpoints: overall survival (OS), toxicity, anemia caused symptoms and influence on cognitive function

Materials & Methods

Study design: prospective, randomized phase III study

Treatment: Patients received 1 of 2 possible adjuvant chemotherapy (CHT) regimens:
TAC: 6 x docetaxel 75 mg/m² + adriamycin 50 mg/m² + cyclophosphamide 500 mg/m², q3w
CEF: 6 x cyclophosphamide 500 mg/m² + epirubicin 100 mg/m² + 5-FU 500 mg/m², q3w

Application of Darbepoetin alfa: Patients were randomized to receive darbepoetin alfa (DA+) 500 µg (q3w) during chemotherapy until the completion of radiotherapy (RT) or to receive standard supportive care alone (DA-, Fig. 1). DA treatment was started at Hb-level ≤13 g/dL (recommendation of the steering committee 01/2008: Hb ≤12 g/dL) and stopped at >14 g/dL (recommendation of the steering committee 01/2008: >12 g/dL).

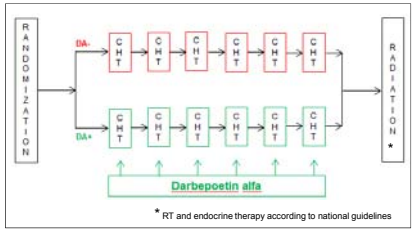

Fig. 1: Study Design

Inclusion criteria:
- primary histologically confirmed breast cancer
- pT1-3, node positive, M0 disease
- free margins, ≥10 surgically removed axillary lymph nodes
- >18 years, ECOG <2

Main exclusion criteria:
- serum creatinine: >1.4 mg/dL, serum bilirubin: TAC >upper normal limit, CEF >2.0 mg/dL
- hematopoetic insufficiency (leukocytes: <3.5 G/l, platelets: <100 G/l)
- inflammatory breast cancer
- surgery >42 days prior to chemotherapy

Statistical methods: Survival analysis was planned after 7 years of study duration. EFS was tested using χ^2-test (α=0.05) with a statistical power of β=80% and log-rank test. Anemia caused symptoms and influence on cognitive function were measured using FACT questionnaires (Functional Assessment of Cancer Therapy (FACT) Quality of Life: FACT-An /FACT-Cog [5]) at beginning of therapy, mid, end of therapy, and at 1 year later.

Results

1234 patients (615 DA+/619 DA-) from 70 centres in Germany were randomized between 01/04 and 06/08 (recruitment time: 4.5 years). 1129 patients received TAC and 105 CEF. In total 1199 patients are available for safety evaluation (DA+/DA-: 598/601), 1170 for intent to treat analysis (ITT; DA+/DA-: 585/585), and 1016 for per protocol analysis (PP; DA+/DA-: 526/490).

Tab. 1: Baseline characteristics (ITT-population)

	DA+ n (%)	DA- n (%)
Age (years, median)	53.0	54.0
Tumor size (cm, median)	2.3	2.3
Positive LN (median)	3.0	3.0
1-3	336 (57.4)	342 (58.5)
≥ 4	249 (42.6)	243 (41.5)
Hormone receptor status		
positive	470 (80.3)	488 (83.4)
negative	114 (19.5)	97 (16.6)
Grading		
1-2	345 (59.0)	368 (62.9)
3	240 (41.0)	217 (37.1)

Baseline characteristics such as nodal status, tumor size, grading and hormone receptor status were well balanced between both study arms slightly favoring the DA- arm.

531 (88.8%) patients in the DA+ arm and 545 (90.7 %) patients in the DA- arm received radiotherapy after chemotherapy according to national guidelines.

Endocrine treatment (tamoxifen and/or aromatase inhibitors) was documented in most (87%) patients with HR+ disease.

Hb-levels: In DA+ treated patients, Hb-levels were stable over the whole treatment period (Fig. 2). In DA- treated patients, Hb-levels decreased during therapy (median of all cycles DA+/DA-: 12.6/11.7 g/dL). There are only 123/7508 cycles with reported Hb-levels above 15 g/dL: DA+ 69 (0.9%) and DA- 54 (0.7%).

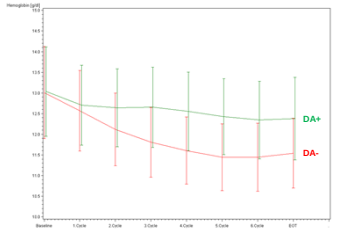

Fig. 2: Hb-levels during therapy

Safety results: During chemotherapy, 286 patients experienced at least one serious adverse event (SAE). Among these 152 patients (25.4%) were in the DA+ study arm and 134 patients (22.3%) in the DA- study arm. SAEs related to DA were mainly thrombosis. In summary 4 cases of pulmonary embolisms (DA+/DA-: 2/2) and 23 thrombosis (DA+/DA-: 17/6, p=0.02) have been reported in both study arms.

Toxicity: The number of reported deaths due to AEs during the chemotherapy was two, both in the DA+ arm (both due to septic multi organ failure). Regarding toxicity profile of the most common AEs according to NCI-CTCAE there are no significant differences between both study arms (Fig. 3).

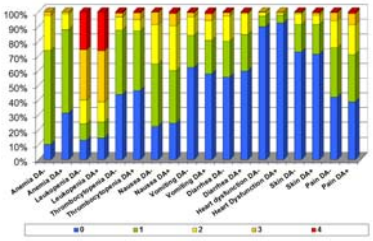

Fig. 3: Toxicity profile per treatment arm

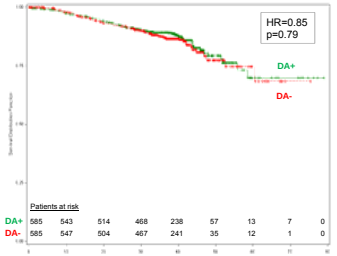

Fig. 4a: EFS – ITT-population

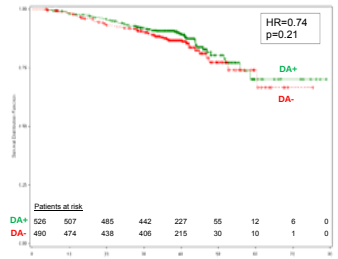

Fig. 4b: EFS – PP-population

Anemia related quality of life: Comparison of FACT-An and FACT-Cog data between study groups revealed no statistically significant difference for any item of the questionnaires.

Event-free survival: The median duration of follow up was 39.6 months in the ITT-population and 39.8 months in the PP-population. Data for the 3-year EFS between DA+ and DA- in the ITT-population were 89.3% and 87.5%, respectively (HR=0.85, p=0.79; Fig. 4a) In the PP-population the data for the 3-year EFS for DA+ and DA- were 90.8% and 87.7%, respectively (HR=0.74, p=0.21; Fig. 4b).

Overall Survival: 3-year OS in the ITT-population was 95.5% and 95.4% for DA+ and DA-, respectively (p=0.89). Comparable values were calculated for the PP-Population.

Unplanned retrospective subgroup analysis (ITT) revealed significantly better EFS for DA+ vs. DA- in the subgroup of HR negative tumors (p=0.03) and no difference within the HR positive subgroup (p=0.73). There is no survival difference according to median Hb-levels (≥12 g/dL vs. <12 g/dL) for all cycles.

Multifactorial analysis revealed nodal involvement, negative hormone receptor status, tumor size >2 cm and tumor grade G3 (vs. G1/2) as significant survival predictors.

Summary and Discussion

- With the proposed scheduling of DA hemoglobin values over 15 g/dL are rare.
- Under chemotherapy baseline Hb-levels are maintained in the DA+ arm and decreased in the DA- arm.
- Anemia grade 2 is less frequent in the DA+ arm (p <0.001).
- DA for prevention of CAA has no significant effect on EFS.
- DA application raises the incidence of thrombosis (DA+: 2.9% vs. DA-: 1%), but not the rate of pulmonary embolism (DA+/DA-: 2/2). There is no therapy related death due to DA application.
- The FACT-An and FACT-Cog data revealed no significant difference between the study arms.

References

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