Anthracycline rechallenge using pegylated liposomal doxorubicin in patients with metastatic breast cancer: a pooled analysis using individual data from four prospective trials

S-E Al-Batran*,1, M Güntner2, C Pauligk1, M Scholz2, R Chen3, B Beiss3, S Stopatschinskaja3, W Lerbs1, N Harbeck4 and E Jäger1

1Klinik für Onkologie und Hämatologie am Krankenhaus Nordwest, Krankenhaus Nordwest, Steinbacher Hohl 2-26, 60488 Frankfurt am Main, Germany; 2Trium Analysis Online GmbH, München, Germany; 3Merck, Kenilworth, NJ, USA; 4Breast Center, University of Cologne, Cologne, Germany

BACKGROUND: The aim of this study was to determine the activity of anthracycline rechallenge using pegylated liposomal doxorubicin (PLD) in patients with metastatic breast cancer (MBC) previously treated with conventional anthracyclines.

METHODS: Pooled individual data from four prospective trials were used, and the primary end point of the pooled analysis was clinical benefit rate (CBR). The studies comprised 935 patients, of whom 274 had received PLD in the metastatic setting after prior exposure to conventional anthracyclines (rechallenge population).

RESULTS: The majority of patients were heavily pretreated. Previous anthracycline therapy was administered in the adjuvant (14%) or metastatic setting (46%), or both (40%). The overall CBR from rechallenge with PLD was 37.2% (95% CI 32.4–42.0). In univariate analyses, the CBR was significantly higher in patients with less exposure to prior chemotherapy, in taxane-naive patients, and in patients with a favourable Eastern Cooperative Group performance status of 0 vs 1 vs 2 (53.3 vs 35.5 vs 18.2%; P<0.001). In multivariate analyses, performance status proved to be the only independent predictor of the CBR achieved with PLD rechallenge (P=0.038). There was no statistically significant difference in CBR regarding the setting, cumulative dose of and/or resistance to prior anthracyclines, or time since prior anthracycline administration.

CONCLUSION: Anthracycline rechallenge using PLD is effective in patients with MBC who have a favourable performance status, regardless of setting, resistance, cumulative dose or time since prior conventional anthracycline therapy.

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In Europe and the United States, breast cancer remains the number one diagnosed cancer in women (incidence rate approximately 28%); and in Europe, it is the leading cause of death from cancer in women (Ferlay et al, 2007; Jemal et al, 2009). Though the majority of women with early-stage disease receive adjuvant systemic treatment to prevent disease recurrence, approximately 30–70% of patients develop metastatic breast cancer (MBC) (Early Breast Cancer Trialists’ Group, 2005; Cardoso et al, 2009). MBC patients represent a very heterogeneous population, and the number of available therapies for MBC is rapidly growing. Anthracyclines and taxanes remain the most active cytotoxic agents in the treatment of this disease, and as such, have been widely integrated into adjuvant regimens for early-stage breast cancer (Early Breast Cancer Trialists’ Group, 2005; Beslija et al, 2009; Cardoso and Castiglione, 2009; Cardoso et al, 2009).

Clinicians still face a significant challenge in the choice of treatment for patients with MBC who have failed one or more chemotherapy regimens. The repeated use of conventional anthracyclines is still believed to be limited by cumulative cardiac toxicity (Jones et al, 2006; Ryberg et al, 2008). Doxorubicin cardiotoxicity is dose dependent. The average incidence of doxorubicin-related cardiotoxicity is 5.1% in women who have received cumulative doses of 400 mg m⁻² (Von Hoff et al, 1979; Swain et al, 2003). The incidence of cardiotoxicity exponentially increases with a cumulative dose of 500 mg m⁻². This treatment-related cardiotoxicity, specifically linked to anthracycline use in these patients, has remained a challenge for physicians, and thus research in this area is increasing.

Because the majority of pretreated patients with MBC have been exposed to anthracyclines, either in the adjuvant or metastatic settings, there is a need for a cardiac tolerable and effective approach. Pegylated liposomal anthracycline formulations, such as pegylated liposomal doxorubicin (PLD, Caelyx; Schering-Plough, Kenilworth, NJ, USA), represent an attractive option in this setting. Single-agent PLD has repeatedly demonstrated comparable efficacy to doxorubicin, with less cumulative cardiac toxicity and less myelosuppression (Gabizon and Martin, 1997; O’Shaughnessy, 2003; Keller et al, 2004; O’Brien et al, 2004; Theodoulou and Hudis, 2004). Moreover, data suggest efficacy of PLD in the anthracycline rechallenge setting (Keller et al, 2004; O’Brien et al, 2004; Al-Batran et al, 2006a, b; Trudeau et al, 2009).

There is no consensus about which parameters should be used in the decision regarding anthracycline rechallenge. Criteria
clinicians need to consider include prior anthracycline treatment, prior taxane exposure, previous radiation, patient performance status, cardiac history and cardiac function, age and other co-variants. Two important factors, time since prior anthracycline therapy and cumulative dose of anthracycline, have been identified as predictive factors for the efficacy of anthracycline rechallenge in some studies; however, they have not been validated (Singal and Iliškovic, 1998).

Thus, we conducted a pooled analysis on individual patient data of MBC populations who received single-agent PLD rechallenge after previous exposure to conventional anthracyclines. The primary objective was clinical benefit rate (CBR). The secondary objective was to determine clinical factors that may predict the efficacy of PLD in anthracycline-pretreated patients with MBC.

MATERIALS AND METHODS

Literature search and identification of studies

The aim of this study was to identify all relevant published prospective randomised clinical trials evaluating PLD as monotherapy in patients with MBC. A literature search was performed using databases (PubMed, CANCERLIT, the Cochrane Library and clinicaltrials.gov).

Study selection

Eligible trials were prospective, in which patients received single-agent PLD for metastatic disease and included at least a subgroup of patients who had been pretreated with conventional anthracyclines. Four trials were identified from these searches for inclusion (Table 1; Keller et al, 2004; O’Brien et al, 2004; Al-Batran et al, 2006a, b). The databases of these studies were provided by Merck, formerly Schering Plough Corp. The analysis was performed with the permission of the ethics committee responsible for our institution.

Study objectives and data extraction

The primary end point, CBR, was defined as objective response, partial response or stable disease lasting longer than 6 months. Rechallenge with PLD was considered efficacious if the CBR exceeded 30%, whereas below 20% was considered inactive. The rate of 30% was considered clinically relevant taking into account the heavily pretreated population. Post hoc calculations provided 98% power to detect a CBR rate >30% (A’Hern, 2001).

Pre-specified clinical parameters, including baseline Eastern Cooperative Oncology Group. aIncluding chemotherapy and hormonal therapy in the adjuvant and metastatic setting.

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**Table 1** Trial characteristics

|                         | Al-Batran et al (2006a) | Al-Batran et al (2006b) | Keller et al (2004) | O’Brien et al (2004) |
|-------------------------|-------------------------|-------------------------|---------------------|---------------------|
| Date first patient enrolled | May 2000                | October 2001            | June 1997           | June 1998           |
| No. of patients         | 79/79/79                | 46/46/33                | 301/150/124         | 509/254/38          |
| Total/received PLD/received PLD after prior CAC | 79/79/79 | 46/46/33 | 301/150/124 | 509/254/38 |
| Study design            | Non-randomised phase II | Non-randomised phase II | Randomised phase III with PLD vs comparator a | Randomised phase III with PLD vs doxorubicin |
| Study population        | Women with at least 1 prior chemotherapy for MBC | Women with at least 1 prior chemotherapy for MBC | Women with taxane refractory MBC and ≤ 2 prior chemotherapies for metastatic disease | Women, previously untreated for metastatic disease |
| Response assessment scale | WHO 50 mg·m⁻² every 4 weeks | WHO 40 mg·m⁻² every 4 weeks | NK 50 mg·m⁻² every 4 weeks | WHO 50 mg·m⁻² every 4 weeks |
| PLD schedule            |                         |                         |                     |                     |

Abbreviations: PLD = pegylated liposomal doxorubicin; MBC = metastatic breast cancer; CAC = conventional anthracycline; WHO World Health Organization; NK = not known. aVincristine or mitomycin C plus vinblastine.

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Anthracycline rechallenge with PLD for MBC

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Table 2 Distribution of predefined clinical parameters

| Predefined clinical parameter                              | N (%) |
|-------------------------------------------------------------|-------|
| Age                                                         |       |
| 18–65 years                                                 | 222 (81.0) |
| >65 years                                                   | 52 (19.0) |
| ECOG performance status                                    |       |
| 0                                                           | 75 (27.4) |
| 1                                                           | 154 (56.2) |
| 2                                                           | 44 (16.0) |
| Unknown                                                     | 1 (0.4) |
| No. of prior therapies                                       |       |
| 1                                                           | 18 (6.6) |
| 2                                                           | 62 (22.6) |
| >2                                                          | 194 (70.8) |
| Previous taxane                                             |       |
| Yes                                                         | 198 (72.3) |
| No                                                          | 66 (24.1) |
| Unknown                                                     | 10 (3.6) |
| Anthracycline-free interval                                 |       |
| 0–12 months                                                 | 96 (35.1) |
| >12 months                                                  | 150 (54.7) |
| Unknown                                                     | 28 (10.2) |
| Setting of prior anthracycline exposure                     |       |
| Adjuvant only                                               | 38 (13.9) |
| Metastatic only                                             | 126 (46.0) |
| Both                                                        | 110 (40.1) |
| Cumulative dose of prior anthracycline                      |       |
| <180 mg·m⁻²                                                 | 79 (28.8) |
| 180–250 mg·m⁻²                                              | 73 (26.7) |
| >250 mg·m⁻²                                                 | 88 (32.1) |
| Unknown                                                     | 34 (12.4) |
| Anthracycline resistance                                    |       |
| Yes                                                         | 118 (43.1) |
| No                                                          | 138 (50.4) |
| Unknown                                                     | 18 (6.5) |

Abbreviations: ECOG = Eastern Cooperative Oncology Group. aIncluding chemotherapy and hormonal therapy in the adjuvant and metastatic setting.

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Statistical analysis

Heterogeneity between studies was tested using the log-rank test for PFS and OS and the Fisher’s exact test for CBR, RR and baseline parameters. The same statistical tests and models were applied to assess the univariate relationship between predefined variables and the primary and secondary end points. Furthermore, Cox proportional hazard models and logistic regression models were used for the multivariate analysis. In a secondary analysis, the univariate results were adjusted for baseline performance status, prior taxane therapy and number of previous chemotherapy regimens (these factors were found to be heterogeneous among the populations). Time-to-event curves was calculated by the Kaplan–Meier method. All \( P \)-values were two sided, with \( P \)-values \(<0.05\) considered to indicate statistical significance.

RESULTS

Characteristics of the patients

Of the 935 patients included in this analysis, 274 (29.3%) received PLD and had at least one prior conventional anthracycline therapy. The distribution of the predefined clinical parameters in the pooled population is shown in Table 2. The median age of the patients was 56 years (range, 29–87 years). Patients had a median of 3.5 prior treatment lines (range, 1–9), and 93.4% had at least two previous therapies (including chemotherapy and hormonal therapy). Prior anthracycline therapy was mostly administered in the metastatic setting, with prior anthracycline being adjuvant (14%), metastatic (46%) or in both settings (40%). Patients received a median of three cycles of PLD (range, 1–18), with a median dose of 83.8 mg per cycle and a mean cumulative dose of

Table 3: Clinical benefit rate

| Variable | Overall | All-Batran et al (2006a) | All-Batran et al (2006b) | Keller et al (2004) | O’Brien et al (2004) |
|----------|---------|-------------------------|-------------------------|---------------------|---------------------|
| No. of patients | 274 | 79 | 33 | 124 | 38 |
| CBR, n (%) | 102 (37.2) | 30 (38.0) | 8 (24.2) | 37 (29.8) | 27 (71.1) |
| 95% CI | 32.4–42.0 | 29.0–47.0 | 12.0–36.5 | 23.1–36.6 | 59.0–83.2 |
| No CBR, n (%) | 170 (62) | 49 (62) | 25 (75.8) | 85 (68.5) | 11 (28.9) |
| NE, n (%) | 2 (0.7) | — | — | 2 (1.6) | — |

Abbreviations: CBR = clinical benefit rate; CB = clinical benefit; NE = not evaluable for clinical benefit.

Table 4: Univariate analysis of outcomes according to clinical parameters

| Variable | CBR, n (%) | P-value | RR, n (%) | P-value | Median PFS (months) | P-value | Median OS (months) | P-value |
|----------|------------|---------|-----------|---------|---------------------|---------|-------------------|---------|
| Age | | | | | | | |
| 18–65 years | 83/220 (37.7) | 0.001 | 17/172 (15.1) | 0.038 | 26/172 (15.1) | 0.049 | 10.7 | 0.632 |
| > 65 years | 19/52 (36.5) | 1 | 8/38 (21.1) | 0.038 | 8/38 (21.1) | 0.038 | 11.9 | 0.632 |
| ECOG performance status | | | | | | | |
| 0 | 40/75 (53.3) | 0.012 | 17/59 (28.8) | 3.4 | 17/59 (28.8) | 3.4 | 15.5 | 0.001 |
| 1 | 54/152 (35.5) | 0.001 | 14/122 (11.5) | 0.638 | 14/122 (11.5) | 0.638 | 11.4 | 0.001 |
| 2 | 8/44 (18.2) | 0.001 | 3/28 (10.7) | 0.001 | 3/28 (10.7) | 0.001 | 1.7 | 0.001 |
| No. previous chemotherapies | | | | | | | |
| 1 | 10/18 (55.6) | 0.913 | 4/16 (25.0) | 0.913 | 4/16 (25.0) | 0.913 | 4.3 | 0.023 |
| 2 | 15/61 (24.6) | 0.001 | 8/55 (14.5) | 0.001 | 8/55 (14.5) | 0.001 | 2.9 | 0.023 |
| > 2 | 77/193 (39.9) | 0.024 | 22/139 (15.8) | 0.024 | 22/139 (15.8) | 0.024 | 3.1 | 0.041 |
| Previous taxane | | | | | | | |
| Yes | 59/196 (30.1) | 0.001 | 17/146 (11.6) | 0.001 | 17/146 (11.6) | 0.001 | 9.9 | 0.023 |
| No | 35/66 (53.0) | 0.001 | 14/56 (25.0) | 0.001 | 14/56 (25.0) | 0.001 | 4.3 | 0.023 |
| Setting of prior anthracycline | | | | | | | |
| Adjuvant | 13/36 (36.1) | 0.001 | 2/30 (6.7) | 0.001 | 2/30 (6.7) | 0.001 | 8.5 | 0.023 |
| Metastatic | 53/126 (42.1) | 0.001 | 24/102 (23.5) | 0.001 | 24/102 (23.5) | 0.001 | 11.9 | 0.023 |
| Both | 36/110 (32.7) | 0.332 | 8/78 (10.3) | 0.050 | 8/78 (10.3) | 0.050 | 2.6 | 0.049 |
| Cumulative dose prior anthracycline | | | | | | | |
| < 180 mg m2 | 26/77 (33.8) | 0.001 | 10/59 (16.9) | 0.001 | 10/59 (16.9) | 0.001 | 9.3 | 0.023 |
| 180–250 mg m2 | 27/73 (37.0) | 0.001 | 8/55 (14.6) | 0.001 | 8/55 (14.6) | 0.001 | 11.9 | 0.023 |
| > 250 mg m2 | 31/88 (35.2) | 0.012 | 8/73 (11.0) | 0.012 | 8/73 (11.0) | 0.012 | 11.2 | 0.041 |
| Anthracycline-free interval | | | | | | | |
| 0–12 months | 28/96 (29.2) | 0.001 | 9/74 (12.2) | 0.001 | 9/74 (12.2) | 0.001 | 2.6 | 0.049 |
| > 12 months | 61/150 (40.7) | 0.078 | 20/120 (16.7) | 0.078 | 20/120 (16.7) | 0.078 | 3.2 | 0.049 |
| Anthracycline resistance | | | | | | | |
| Yes | 47/138 (40.5) | 0.001 | 18/91 (19.8) | 0.001 | 18/91 (19.8) | 0.001 | 11.3 | 0.023 |
| No | 47/116 (34.1) | 0.001 | 14/104 (13.5) | 0.001 | 14/104 (13.5) | 0.001 | 11.1 | 0.023 |

Abbreviations: CBR = clinical benefit rate; CB = clinical benefit; NE = not evaluable for clinical benefit.
311 mg (range, 25.5–1394 mg). There was significant heterogeneity between the studies regarding baseline ECOG performance status, taxane pretreatment and number of prior chemotherapy regimens. This heterogeneity was found to be attributed to the study by O’Brien et al (2004), which enrolled patients previously untreated in the metastatic setting (Table 1).

Overall clinical benefit rate

Clinical benefit rate is shown in Table 3 (O’Brien et al, 2004; Keller et al, 2004; Al-Batran et al, 2006a, b). The overall CBR was 37.2% (95% CI, 32.4–42.0). The lower boundary of the 95% confidence interval of the CBR observed was above the pre-defined 30% rate. The logistic regression model showed a higher CBR in the study by O’Brien ($P < 0.001$) as compared with the study by Keller. In the pooled population, median PFS and OS were 3 (95% CI, 2.8–3.7 months) and 11.1 months (95% CI, 8.9–13.1 months), respectively.

Outcomes according to clinical parameters: univariate analyses

Clinical benefit rate, RR, PFS and OS according to clinical parameters are shown in Table 4. There was no difference in CBR between patients who were considered anthracycline resistant and those who were not (40.5% vs 34.1%; $P = 0.300$). There was also no difference in CBR between patients who received prior anthracycline in the adjuvant setting (34.2%), in the metastatic setting (42.1%), or both settings (32.7%), $P = 0.332$. There were no significant differences in CBR between patients who had low, medium or high cumulative doses of prior anthracycline at baseline (33.8% vs 37.0% vs 35.2%, respectively; $P = 0.913$). A trend towards higher CBR was detected in patients who received PLD >12 months vs $\leq$12 months since the end of their prior anthracycline therapy (40.7% vs 29.2%; $P = 0.078$). The adjustment for ECOG performance status, taxane pretreatment and number of prior chemotherapies revealed similar results (data not shown).

Among clinical parameters not associated with prior anthracycline therapy, ECOG performance status was the strongest predictor of clinical benefit; CBR was 53.3, 35.5 and 18.2% in patients with ECOG performance status of 0, 1 and 2, respectively ($P < 0.001$). In addition, a statistically significant higher RR, longer PFS and OS were observed for patients with ECOG performance status of 0 and 1 vs 2 (Table 4; Figure 1). Significantly higher CBRs were also observed in taxane-naive patients (53.0%) vs patients who received a previous taxane (30.1%), $P = 0.001$, and in patients who failed only one therapy vs more than one therapy (1 vs 2 vs 3: 55.6% vs 24.6% vs 39.9%, respectively; $P = 0.024$). Age was not a predictor of CBR. The univariate results regarding CBR were adjusted for ECOG performance status, taxane pretreatment and number of prior chemotherapies using a logistic regression model. The results were similar to the unadjusted models (data not shown).

Multivariate analyses

All clinical parameters were included in a logistic regression model to determine their predictive effect on CBR. ECOG performance status was a strong predictor of CBR ($P = 0.038$). The number of prior chemotherapies was no longer a significant predictor of CBR ($P = 0.192$), and taxane pretreatment showed a non-significant trend ($P = 0.072$). None of the other clinical parameters was statistically significant. In a multivariate Cox regression analysis, ECOG performance status also was a significant predictor of PFS ($P = 0.002$) and OS ($P < 0.001$). The number of prior chemotherapies was a significant predictor of OS ($P = 0.041$).

DISCUSSION

This pooled analysis on the largest data set of MBC patients who were pretreated with an anthracycline evaluates the efficacy of anthracycline rechallenge using PLD. All patients had received conventional anthracyclines, and 72% had received prior taxane therapy. The majority were pretreated with more than one line of chemotherapy for metastatic disease. Therefore, most patients in this analysis were in an advanced and palliative course of their disease when they received PLD as an anthracycline rechallenge. Accordingly, we chose CBR as the primary end point for this patient population rather than RR or PFS (Ohorodnyk et al, 2009).
A clinical benefit is achieved when either an objective response or a long-lasting stable disease is documented. This reflects a direct and real effect of the rechallenge. Overall survival was not selected as the primary objective because it is influenced by other parameters such as further therapies and prognostic factors (Saad et al, 2010). The primary assumption of this study, that CBR > 30%, was met in this analysis, where 37.2% of patients exhibited a clinical benefit from rechallenge with PLD (95% CI, 32.4–42.0). In the univariate analysis, patients with less exposure to prior treatment (i.e., one prior regimen or taxane-naïve) exhibited a statistically significantly higher CBR (53–56%) than patients with a prolonged disease-free interval. These results translate into an expected CBR of 37% observed in first-line patients, and 34 and 71% in patients previously treated with a single-agent therapy. Furthermore, the incidence of severe palmar-plantar erythrodysesthesia and mucositis in a prospective multicenter phase II trial with pegylated liposomal doxorubicin in patients with metastatic breast cancer previously treated with conventional anthracyclines: a multicentre phase II trial. Br J Cancer 94: 1615–1620 Al-Batran SE, Meepholth HG, von Minckwitz G, Atmaca A, Kleeberg U, Meuthen I, Morack G, Verbeek D, Sehouli J, Knuth A, Jager E (2006a) The clinical benefit of pegylated liposomal doxorubicin in patients with metastatic breast cancer previously treated with conventional anthracyclines: a multicentre phase II trial. Br J Cancer 94: 1615–1620 Al-Batran SE, Kühnel J, von Minckwitz G, Atmaca A, Kleeberg U, Harbeck N, Morack G, Verbeek D, Sehouli J, Knuth A, Jager E (2006b) Reduced incidence of severe palmar-plantar erythrodysesthesia and mucositis in a prospective multicenter phase II trial with pegylated liposomal doxorubicin at 40 mg/m² every 4 weeks in previously treated patients with metastatic breast cancer. Oncology 70: 141–146 Beslija S, Bennetlouf V, Guin HJ, Heijmans V, Jassim M, Koster J, Kölster WJ, Kranier M, Menard S, Petti T, Petruzella L, Possinger K, Schmid P, Stadtmayer E, Stockler M, Van Belle S, Vogel C, Wilcken N, Wittsche C, Zieleinski CC, Zwierzina H (2009) Third consensus on medical treatment of metastatic breast cancer. Ann Oncol 20: 1771–1785 Blum JL, Dees EC, Chacko A, Doane L, Ehrirajan S, Hopkins J, McMahon R, Merten S, Negron A, Neubauer M, Leggodi D, Boehm KA, Asmar L, O’Shaughnessy JA (2006) Phase II trial of capecitabine and weekly paclitaxel as first-line therapy for metastatic breast cancer. J Clin Oncol 24: 4384–4390 Cardoso F, Bedard PL, Winer EP, Pagani O, Senkus-Konefka E, Fallowfield LJ, Kyriakides S, Costa A, Cufet T, Albain KS (2009) International guidelines for management of metastatic breast cancer: combination vs sequential single-agent chemotherapy. J Natl Cancer Inst 101: 1174–1181 Cardoso F, Castiglione M (2009) Locally recurrent or metastatic breast cancer: ESMO clinical recommendations for diagnosis, treatment and follow-up. Ann Oncol 20(Suppl. 4): 15–18 Ciruelos EM, Cortés J, Cortés-Funes H, Mayordomo JI, Bermejo O, Ojeda B, García E, Rodríguez CA, Muñoz M, Gómez P, Manso L, Andrés R, Lluch A, Saura C, Mendiola C, Baselga J (2010) Gemcitabine and capecitabine in previously anthracycline-treated metastatic breast cancer: a multicenter phase II study (SOLT 0301 trial). Ann Oncol 21: 1442–1447 Early Breast Cancer Trials’ Group (2005) Effects of chemotherapy and hormonal therapy for early breast cancer on recurrence and 15-year survival: an overview of the randomized trials. Lancet 365: 1687–1717 Feltay J, Autier P, Boniol M, Heanue M, Colombet M, Boyle P (2007) Estimates of the cancer incidence and mortality in Europe in 2006. Ann Oncol 18: S81–S92.
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