Comparison of adjuvant ED and EC-D regimens in operable breast invasive ductal carcinoma

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Abstract. In China, the adjuvant epirubicin and docetaxel (ED) regimen is widely used as a substitute for the epirubicin and cyclophosphamide followed by docetaxel (EC-D) regimen in patients with operable breast cancer. However, their equivalence has not yet been demonstrated. This retrospective study compared these two adjuvant regimens as regards feasibility, safety and efficacy. Data on consecutive patients who received either ED (70/75 mg/m2 every 3 weeks for 6 cycles) or EC-D (70/600 mg/m2 epirubicin/cyclophosphamide followed by 75 mg/m2 docetaxel every 3 weeks for 4 cycles each) as their adjuvant chemotherapy in our center from January 2009 to January 2014, were analyzed. A total of 374 patients was enrolled, among whom 250 patients received the ED regimen, and 124 patients received the EC-D regimen. The overall median follow-up time was 38.6 months. In total, 90 and 94.4% of patients in the ED and EC-D groups, respectively, completed full cycles of chemotherapy (P=0.174). There was no difference in efficacy in terms of disease-free survival (DFS) and overall survival (OS) (DFS, P=0.919; OS, P=0.069). The incidence of neutropenia in the ED group was similar to that in the EC-D group (81.2 vs. 78.9%, P=0.660) with a similar utilization rate of granulocyte-colony stimulating factor (G-CSF; 76.9 vs. 75.2%, P=0.850). However, grade 3/4 gastrointestinal reactions were more frequently observed in the patients who received the EC-D regimen (42.0 vs. 29.2%, P=0.058). The findings of our study indicate that with similar feasibility, safety and mid-term efficacy, the adjuvant ED regimen for 6 cycles may be an alternative to the EC-D regimen in operable breast cancer.

Introduction

Breast cancer is the most common malignancy affecting the female population, accounting for approximately 1/4 of all cancers (1). China, a country that has had a low incidence rate of breast cancer in the past, has been confronted with increasing breast cancer morbidity in recent years (2,3). Adjuvant chemotherapy, with its great efficacy in eradicating residual carcinoma, and thereby lowering the risk of recurrence and metastasis, has become an indispensable treatment for early-stage breast cancer (4). In China, adjuvant chemotherapy is widely used, but is completed at a suboptimal rate. Even in Beijing, a highly developed city in which China’s best medical resources are available, 12.1% of patients who commence adjuvant chemotherapy receive <4 cycles of chemotherapy (5).

The addition of docetaxel to anthracycline-based therapy demonstrated superiority to the temporal standard doxorubicin and cyclophosphamide (AC) regimen in terms of survival in metastatic breast cancer (MBC) (6), rendering the epirubicin and docetaxel (ED) regimen among the most active therapeutic regimens for MBC. In neoadjuvant chemotherapy (NAC), 6 cycles of the ED regimen have been shown to result in a higher pathological complete response rate and this was thus considered a standard regimen (7). However, in adjuvant chemotherapy, epirubicin and cyclophosphamide followed by docetaxel (EC-D) as the standard regimen for concurrent administration has been proven to be less effective with the addition of taxanes to anthracyclines (8-10). Despite this fact, 6 cycles of adjuvant ED has been applied as a substitute for 8 cycles of EC-D in China. However, this issue is still under debate as there is a lack of evidence for similar comparisons between the regimens. The ED regimen is favored for its shorter course and fewer hospitalizations, which are presumed to improve the unsatisfactory completion of chemotherapy.

In this study, to investigate whether the ED regimen for 6 cycles may be a substitute for the EC-D regimen in adjuvant chemotherapy, we performed a retrospective analysis to compare its feasibility, efficacy and safety.

Patients and methods

Patients. Data on patients who received either the ED or EC-D regimen after curative surgery at Qilu Hospital of
Shandong University (Shandong, China) from January 2009 to January 2014 were reviewed. Follow-up information, including the completion status of post-operative adjuvant therapy, treatment-related side-effects (mainly as regards hematological toxicities and gastrointestinal reactions of chemotherapy), outcomes (recurrence, metastasis, invasive contralateral breast cancer and death from any cause), was collected regularly via telephone contact and the outpatient department.

The ED regimen was prescribed as 70 mg/m² epirubicin and 75 mg/m² docetaxel at a 3-week interval for 6 cycles. The EC-D regimen was prescribed as 70 mg/m² epirubicin and 600 mg/m² cyclophosphamide followed by 75 mg/m²/docetaxel at a 3-week interval for 4 cycles each. Primary prophylaxis with granulocyte-colony stimulating factor (G-CSF) was not advised unless neutropenia had previously occurred. G-CSF measurements were used if the white blood cell (WBC) count was <3x10⁹/l. Patients who received the ED or EC-D regimen were designated as the ED or EC-D groups, respectively.

During the follow-up evaluation, we noted that some patients converted to the EC-D regimen after 1 or 2 cycles of the ED regimen or the cyclophosphamide, epirubicin and 5-fluorouracil (CEF) regimen, despite no intolerable treatment-related toxicities. Only a few patients strictly completed the aforementioned EC-D regimen. Thus, we placed patients who converted to the EC-D regimen without presenting with intolerable toxicities in the EC-D group. Patients who received NAC or were diagnosed with systemic metastasis at initial presentation were excluded.

Statistical analysis. The primary end-point was disease-free survival (DFS), which was defined as the time from surgery to local recurrence, metastasis, or diagnosis of a second primary cancer or invasive contralateral breast cancer. Patients with incomplete follow-up or without a documented DFS event were censored at the date that they were last known to be alive. Overall survival (OS) was defined as the time from the date of surgery to death from any cause. Neutropenia was defined as an absolute WBC count <3x10⁹/l.

The continuous data were compared using the Student’s t-test. Categorical data were analyzed using Fisher’s exact test. The Kaplan-Meier method was used to estimate the DFS and OS distributions, and the log-rank test was used to detect differences in these distributions with respect to treatment. Cox proportional hazards models were used to estimate the effects of treatment alone and the effects of treatment after adjusting for some of the baseline co-variates. The Wald test was used to test for significant co-variates in the proportional hazards models. Toxicity was graded according to the National Cancer Institute Common Toxicity Criteria (version 3.0). For all the statistical tests, a value of P<0.05 was considered to indicate a statistically significant difference, and all P-values were two-sided. Data analysis was performed using SPSS version 18.0 (SPSS, Inc., Chicago, IL, USA).

Results

Patient characteristics. In total, 374 individuals were enrolled in this study (250 patients in the ED group and 124 patients in the EC-D group). The clinicopathological characteristics of the patients and immunohistochemical analysis are illustrated in Table I. The distribution of most characteristics was well balanced between the two groups apart from the estrogen receptor (ER)/progesterone receptor (PR) status.

The overall median follow-up time was 38.6 months (range, 13-72 months), with follow-up times of 39.4 and 38.1 months for the ED and EC-D groups, respectively. The EC-D group consisted of 43 patients who strictly adhered to the EC-D regimen, 77 patients who converted to EC-D therapy after receiving 1 cycle of the ED regimen (ED*1, EC*3, D*4), 3 patients who converted to the EC-D regimen after 2 cycles of the ED regimen (1 patient received ED*2, EC*3, D*3, and the remaining 2 patients received ED*2, EC*2, D*4) and 1 patient who converted from the CEF to the EC-D regimen during the second cycle (CEF*1, EC*3, D*4). However, the ED group did not consist of patients who converted to EC therapy from other regimens. Four human epidermal growth factor receptor 2 (HER2)-positive patients were treated with herceptin for 1 year in the ED group, and 15 patients in the EC-D group received 1 year of herceptin treatment.

Completion status. Approximately 10 and 5.6% of the patients failed to complete the chemotherapy program in the ED and EC-D groups, respectively. The reasons for therapeutic termination are listed in Table II. There was no significant difference in the completion status between the treatment groups (90% for ED vs. 94.4% for EC-D, P=0.174). The percentage of patients who quit the program due to severe toxicities did not differ significantly between the 2 groups (5.6% for ED vs. 3.2% for EC-D, P=0.443).

DFS and OS. The number of metastatic events and deaths in both groups are summarized in Table III. In total, 2 breast cancer-related deaths and 4 recurrences were observed in the patients who failed to complete ED chemotherapy. All 5 recurrences occurred in patients who completed the EC-D therapy.

Among all the patients who completed the therapy (n=342), there were 10 DFS events in the ED group and 5 in the EC-D group. DFS Kaplan-Meier curves for each treatment group are illustrated in Fig. 1. No significant differences in DFS were observed between the two treatments [hazard ratio (HR) for EC-D vs. ED, 0.947, 95% confidence interval (CI): 0.327-2.744; P=0.919; Table IV]. When adjusting for age, menopausal status, tumor size, tumor grade, ER/PR status and nodal status, there were still no significant differences in DFS between the two treatment groups (HR for EC-D vs. ED, 0.694, 95% CI: 0.206-2.345; P=0.557; Table IV). When all the patients (n=374) were analyzed, there were 14 events in the ED group and 5 events in the EC-D group. The effect of the two treatments on DFS still exhibited no significant difference between the 2 groups (HR for EC-D vs. ED, 0.736, 95% CI: 0.283-1.913; P=0.529; Table IV). The DFS Kaplan Meier curves for the ED group and the EC-D subgroups with or without a therapy change are shown in Fig. 2, demonstrating no significant difference in DFS between the ED group and the two subgroups of the EC-D group (P=0.909). Fig. 3 illustrates the effect of treatment on DFS in the subgroups with different baseline characteristics. None of the interactions between treatment and baseline characteristics were statistically significant.

There were 6 deaths among the patients who completed ED chemotherapy. In the EC-D group, no patients died (Table III).
Table I. Clinicopathological characteristics of the patients enrolled in this study.

| Variables                  | ED (n=250) | EC-D (n=124) | P-value |
|---------------------------|------------|--------------|---------|
| Age, years                | 47.45±8.65 | 48.57±10.10  | 0.345   |
| Age group                 |            |              |         |
| <50                       | 157 (62.8) | 76 (61.3)    | 0.821   |
| ≥50                       | 93 (37.2)  | 48 (38.7)    |         |
| Menopausal status         |            |              | 0.422   |
| Pre-menopausal            | 165 (66.0) | 76 (61.3)    |         |
| Post-menopausal           | 85 (34.0)  | 48 (38.7)    |         |
| Tumor size                |            |              | 0.438   |
| ≤2 cm                     | 123 (54.0) | 56 (47.9)    |         |
| 2<T≤5 cm                  | 99 (43.4)  | 56 (47.9)    |         |
| T>5 cm                    | 6 (2.6)    | 5 (4.2)      |         |
| Not available             | 22         | 7            |         |
| Pathologic type           |            |              | 0.962   |
| IDC                       | 232 (92.8) | 116 (93.5)   |         |
| ILC                       | 4 (1.6)    | 2 (1.6)      |         |
| IMPC                      | 6 (2.4)    | 2 (1.6)      |         |
| Others                    | 8 (3.2)    | 4 (3.2)      |         |
| Tumor grade               |            |              | 0.667   |
| Low                       | 2 (0.9)    | 0 (0)        |         |
| Intermediate              | 149 (67.7) | 76 (66.1)    |         |
| High                      | 69 (31.4)  | 39 (33.9)    |         |
| Not available             | 30         | 9            |         |
| Counts of positive lymph nodes |       |              | 0.466   |
| 0                         | 124 (49.6) | 64 (51.6)    |         |
| 1-3                       | 74 (29.6)  | 42 (33.9)    |         |
| 4-9                       | 36 (14.4)  | 14 (11.3)    |         |
| ≥10                       | 16 (6.4)   | 4 (3.2)      |         |
| Surgery                   |            |              | 0.358   |
| Modified radical mastectomy | 240 (96.0) | 119 (96.0)   |         |
| Radical mastectomy        | 4 (1.6)    | 2 (1.6)      |         |
| Breast conserving surgery | 4 (1.6)    | 0 (0.0)      |         |
| Nipple-sparing mastectomy | 2 (0.8)    | 3 (2.4)      |         |
| ER status                 |            |              | 0.046   |
| Positive                  | 178 (71.2) | 75 (60.5)    |         |
| Negative                  | 72 (28.8)  | 49 (39.5)    |         |
| PR status                 |            |              | 0.035   |
| Positive                  | 161 (64.4) | 67 (54.0)    |         |
| Negative                  | 89 (35.6)  | 57 (46.0)    |         |
| HER2                      |            |              | 0.155   |
| Positive                  | 55 (24.7)  | 37 (32.5)    |         |
| Negative                  | 168 (75.3) | 77 (67.5)    |         |
| Not available             | 27         |              |         |

ED, epirubicin and docetaxel; EC-D, epirubicin, cyclophosphamide followed by docetaxel; ER, estrogen receptor; PR, progesterone receptor; HER2, human epidermal growth factor receptor 2.

Table II. Patients who failed to complete adjuvant therapy out of the total number of patients in each group.

| Reasons for not completing | ED (n=250) | EC-D (n=124) | P-value |
|----------------------------|------------|--------------|---------|
| Severe toxicity            | 14 (5.6)   | 4 (3.2)      | 0.443   |
| Cardiac symptoms           | 3          | 2            |         |
| Gastrointestinal reactions | 2          | 0            |         |
| Myelosuppression           | 0          | 2            |         |
| Other toxicity             | 9          | 0            |         |
| Other reasons*             | 11 (4.4)   | 3 (2.4)      | 0.403   |
| Total                      | 25 (10.0)  | 7 (5.6)      | 0.174   |

*Other reasons include questioning the efficacy of the therapy or unable to bear the long course of the therapy. ED, epirubicin and docetaxel; EC-D, epirubicin and cyclophosphamide followed by docetaxel.

Figure 1. Kaplan-Meier curve of disease-free survival in the epirubicin and docetaxel (ED) and epirubicin and cyclophosphamide followed by docetaxel (EC-D) groups. Only patients who completed the chemotherapy were analyzed. Solid green curve indicates the ED group; dotted blue curve indicates the EC-D group.

Figure 2. Kaplan-Meier curve of disease-free survival in the epirubicin and docetaxel (ED) group and the 2 epirubicin and cyclophosphamide followed by docetaxel (EC-D) subgroups. Only patients who completed the chemotherapy were analyzed. Solid green curve indicates ED; dotted light blue curve indicates the subgroup without a therapy change in the EC-D group; dotted dark blue curve indicates the subgroup with a therapy change in the EC-D group.
There was no significant difference in OS between the treatment groups (HR for EC-D vs. ED, 0.216, 95% CI: 0.040-1.126; P=0.069; Table IV). After adjustment, there was no significant difference in the OS of these groups (P=0.967). When all the patients were analyzed (n=374), the OS of the ED group was inferior to that of the EC-D group (HR for EC-D vs. ED,
0.221, 95% CI: 0.051-0.959; P=0.044; Table IV). However, after adjustment, the effects of the 2 treatments on OS did not differ significantly (P=0.968).

Toxicity. There was no significant difference in the incidence of neutropenia between the two treatment groups (81.2% with ED vs. 78.9% with EC-D, P=0.660; Table V). The utilization rate of G-CSF was similar between the 2 groups (76.9% with ED vs. 75.2% with EC-D, P=0.850; Table V). To investigate whether this negative result was due to the confounding factor of patients who changed their therapy in the EC-D group, we compared the incidence and usage of G-CSF between the 2 subgroups (with/without changing chemotherapy) of the EC-D group. We found that the incidence of neutropenia and the usage of G-CSF were both similar between the 2 subgroups (P=1.000 for both comparisons, Table VI).

Discussion

This study retrospectively compared the feasibility, survival and common toxicities of the ED and EC-D regimens as adjuvant chemotherapy for patients with operable breast cancer. In total, >90% of the patients completed their chemotherapy in both groups, indicating that both regimens were feasible. Although the addition of adjuvant taxanes has demonstrated an improvement in survival (11), the concurrent use of taxanes and anthracyclines with a shorter course has proven to be a less effective method when compared with sequential administration in adjuvant therapy (8,11,12). In a meta-analysis with all available phase III randomized trials comparing the sequential and concurrent use of taxanes and anthracyclines in adjuvant therapy, Shao et al (8) demonstrated that sequential administration had a more favorable outcome than concurrent treatment. However, this meta-analysis consisted of only 3 randomized trials, including the NSABP B-30, BIG 02-98 and BCIRG-005 trials. Among these trials, the sequential arm with a higher cumulative dose of anthracyclines and taxanes demonstrated superiority in survival (10,13), whereas the sequential arm with a relatively lower cumulative dose of the two drugs showed a more favorable outcome than concurrent treatment.
both of the aforementioned studies showed no inferiority in the short-term therapeutic effects of concurrent treatment, which was consistent with our results.

The concurrent administration of anthracyclines and taxanes has been reported to have more severe hematological toxicities compared to sequential and anthracycline-based regimens (6,16). The primary prophylactic use of G-CSF based on National Comprehensive Cancer Network guidelines for a higher risk of febrile neutropenia (FN) was also recommended (6,17). However, the results of our study suggested that when primary prophylactic G-CSF was not routinely used, the severity of myelosuppression with the ED regimen was similar to that with the EC-D regimen on the basis of the identical incidence of neutropenia and the utilization rate of G-CSF, as well as the small number of patients whose treatment was limited by severe myelosuppression. This result could be explained by the timely support of G-CSF and the difference in population susceptibility between Mongolians and Caucasians. The above-mentioned ongoing phase III randomized trial based on Chinese patients comparing ET and EC-T also reported no significant difference in toxicities, including grade 3/4 neutropenia, in their primary results (15). However, another study on Korean patients suggested that the AD regimen was associated with a significantly higher incidence of FN and grade 3/4 neutropenia compared with the AC-T regimen in the neoadjuvant setting (16). The study used docetaxel at a 3-week interval in the AD group and paclitaxel at a 3-week interval in the AC-T group. Docetaxel administered every 3 weeks was proven to be associated with higher grade hematological toxicity compared with paclitaxel administered at a 3-week interval by the E1199 trial (18); the higher incidence of severe toxicity, such as myelosuppression in the AD group was partially due to different taxanes. Moreover, in the BCIRG-005 trial, although the incidence of grade 3/4 neutropenia during the 6 cycles of the TAC arm was significantly higher than that of the AC-T arm (17.4 vs. 7.7%; P<0.001), the incidence of neutropenic infection was similar between the two treatments (8.5% with AC-T vs. 9.7% with AT; P=0.25) (9). Taken together, these studies demonstrated that the ED regimen was safe and feasible with the support of G-CSF.

Our study had several limitations. First, it was a retrospective study with a relatively small sample size, a short follow-up period and few DFS/OS events, which affected the power in comparing the efficacy of the two treatments. Moreover, the EC-D group consisted of a large number of patients who converted to the ED regimen after 1-2 cycles of ED and other regimens, which also reduced the power of the study. Thus, the similarities in efficacy between the two regimens could have arisen by chance. However, the large number of patients who changed from the ED regimen to the EC-D regimen was a reflection of the controversy between these two treatments. Due to the limitations of our study, more credible results are needed from prospective randomized clinical trials. Thus, the final results of the phase III trial performed by Yuan et al (15) are eagerly anticipated. Second, we failed to provide the incidence of grade 3/4 neutropenia and FN, which could directly reflect the severity of myelosuppression in the treatments. However, we could infer from the similarities in the incidence of neutropenia, the usage rate of G-CSF, the start time of the use of G-CSF and the number of patients who quit due to severe hematological toxicity.

| Event                          | EC-D (n=43) | EC-D (n=81) | P-value |
|-------------------------------|-------------|-------------|---------|
| Neutropenia                   |             |             | 1.000   |
| Yes                           | 30 (78.9)   | 56 (78.9)   |         |
| No                            | 8 (21.1)    | 15 (21.1)   |         |
| NA                            | 5           | 10          |         |
| Treatment                     |             |             | 1.000   |
| G-CSF                         | 29 (76.3)   | 53 (74.6)   |         |
| Oral drugs                    | 1 (2.6)     | 3 (4.2)     |         |
| No treatment                  | 8 (21.1)    | 15 (21.1)   |         |
| NA                            | 5           | 10          |         |
| Time to start using G-CSF     |             |             | 0.239   |
| Cycle 1-3                     | 17 (77.3)   | 32 (91.4)   |         |
| 4th cycle or later            | 5 (22.7)    | 3 (8.6)     |         |
| NA                            | 21          | 46          |         |

This subgroup was comprised of patients with a therapy change. bNeutropenia was defined as the blood WBC <3x10^9/l. The percentages were calculated with the unavailable data excluded. GI reactions, gastrointestinal reactions; NA; not available; ED, epirubicin and docetaxel; EC-D, epirubicin and cyclophosphamide followed by docetaxel; G-CSF, granulocyte-colony stimulating factor.
between the treatment groups, that the ED regimen was safe with the proper use of G-CSF.

Despite these limitations, our study, to the best of our knowledge, was the first to compare these two frequently used adjuvant chemotherapy regimens in China. In addition, to perform a more accurate comparison of the efficacy, we investigated whether patients who underwent a therapy change in the EC-D group affected the results by analyzing the survival and toxicity events in the subgroups with or without a therapy change. Considering that the ED group consisted of more ER/PR-positive patients, we calculated the DFS and OS after adjusting for ER/PR status, and no interactions were found between treatment efficacy and the ER/PR status.

In conclusion, according to our results, the completion status and hematological toxicities were similar between the ED and EC-D regimens, while the gastrointestinal tolerance of the ED regimen was better than that of the EC-D regimen. Moreover, the mid-term DFS and OS of the ED regimen were not inferior to the EC-D regimen. Thus, the ED regimen for 6 cycles may be an alternative for the EC-D regimen as postoperative adjuvant chemotherapy for patients with operable breast cancer.

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