Impact of chemotherapy schedule modification on breast cancer patients: a single-centre retrospective study

Gobi Hariyanayagam Gunasekaran1 · Mohamed Azmi Bin Ahmad Hassali2 · Wan Mohd Akmal Bin Wan Sabri1 · Muhammad Tahar Bin Rahman3

Received: 5 September 2019 / Accepted: 7 March 2020 / Published online: 17 March 2020
© Springer Nature Switzerland AG 2020

Abstract

Background Nonconformity to chemotherapy schedules is common in clinical practice. Multiple clinical studies have established the negative prognostic impact of dose delay on survival outcome. Objective This study investigated the prevalence and reason for chemotherapy schedule modifications of breast cancer patients. This study also investigated the impact of schedule modifications on overall survival (OS). Setting This retrospective cohort study was done among breast cancer patient receiving chemotherapy from 2013 to 2017 and patients were followed until 31 Dec 2018. Methods Medical records of patients with cancer were reviewed. Female patients over eighteen years old were included, with primary carcinoma of the breast, who received anthracycline or taxane based chemotherapy regime and completed more than two cycles of chemotherapy. Patients were categorized into three groups of (1) no schedule modification, (2) with schedule modification and (3) incomplete schedule. The Kaplan–Meier was used to test for survival differences in the univariate setting and Cox regression model was used in the multivariate setting. Main outcome measure Prevalence, overall survival rates and hazard ratio of three schedule group

Results Among 171 patient who were included in the final analysis, 28 (16.4%) had no schedule modification, 118 (69.0%) with schedule modification and 25 (14.6%) had incomplete schedule with OS of 75.0%, 59.3% and 52.0% respectively. 94% (189) of all cycle rescheduling happened because of constitutional symptoms (70), for non-medical reasons (61) and blood/bone marrow toxicity (58). When compared to patients with no schedule modification, patients with schedule modification had a 2.34-times higher risk of death (HR 2.34, 95% CI 1.03–5.32; \( p = 0.043 \)). Conclusion Nonconformity to the chemotherapy schedule is common in clinical practice because of treatment complications, patients’ social schedule conflicts, and facility administrative reasons. Cumulative delays of \( \geq 14 \) days are likely to have negative prognostic effect on patient survival. Thus, the duration of the delays between cycles should be reduced whenever possible to achieve the maximum chemotherapeutic benefit.

Keywords Breast cancer · Chemotherapy · Hazard ratio · Overall survival · Schedule modification

Impact on practice statements

- Patients should be counselled to expect more visits to the hospital in the event of treatment toxicity because the chemotherapy cycle will be rescheduled until the patient’s investigational value are satisfactory for subsequent chemotherapy administration
- While rescheduling chemotherapy is warranted the physician should consider continuing the subsequent chemotherapy session within 5–7 days if the patient is clinically well to reduce the cumulative duration of the delay
- Pharmacists should log the duration between the chemotherapy cycle and advise physicians on subsequently
scheduled chemotherapy dates to ensure that the time between cycles and the total duration of the chemotherapy regimen conforms to the clinical regimen.

Introduction

Over the last three decades, treatment paradigms for breast cancer have evolved, and the introduction of new cytotoxic agents have made chemotherapy a main treatment modality for breast cancer along with surgery and radiotherapy [1–3]. The superior survival benefit of chemotherapy for female breast cancer patients was demonstrated by a meta-analysis of 123 studies that reported a 21% reduction in mortality (Relative risk (RR) 0.79, 95% confidence interval [CI] 0.72–0.85) with an absolute 10-year gain of 6.5% among 100,000 patients [2]. However, the aforementioned benefit of chemotherapy was evaluated from randomised clinical trials where strict adherence to the chemotherapy schedule was required. In clinical practice, chemotherapy schedule modifications occur routinely for medical-related complications or non-medical reasons such as a patient’s social schedule or a facility administrative reason. A large multicentre study compromising 1243 oncology centres in the USA reported that 24.9% of patients receiving chemotherapy experienced schedule modification of ≥ 7 days [4] while Wu et al. reported that 8.2% of 47,159 patients from a community oncology database had their chemotherapy duration extended by 17 ± 8 days [5].

Schedule modification contributes to nonconformity to the clinical trial protocol, which established the survival benefit of a particular chemotherapy regimen [6–11]. Consequently, several studies have reported a lower survival rate among chemotherapy-sensitive tumour patients who experienced dose delay and schedule modification [12–14]. For example, Liutkauskiene et al. reported that patients who experienced a chemotherapy schedule modification had a 3.3-times higher risk of death compared with patients who did not experience any chemotherapy schedule modifications (Hazard ratio (HR) 3.3, 95% CI 1.2–8.5, p = 0.016) [13].

However, the above studies associated a negative prognostic effect of schedule modification with survival for early stage breast cancer where chemotherapy is given with curative intent. The impact of schedule modification on overall survival (OS) and traditional prognostic factors for a neoadjuvant or palliative modality are relatively unknown. Understanding chemotherapy schedule modification is one research area that may help to improve breast cancer survival.

Aim of the study

This study aims to investigate the prevalence of chemotherapy schedule modification and to analyse the reason for schedule modification and duration of the delay (in days). This study also aims to investigate the impact of schedule modification on OS and the hazard of death among breast cancer patients.

Ethics approval

Ethics approval to conduct the study was obtained from the Medical Ethical Review Committee [MERC KKM. NIH-SEC. P18-1872(6)], Ministry of Health, Malaysia.

Methods

Study setting

This retrospective cohort study was conducted among female breast cancer patients receiving chemotherapy for cancer treatment in Hospital Seri Manjung, Malaysia from January 2013 to December 2017, and patients were followed until 31 December 2018. Data for this study were obtained from the patient medical documentation and chemotherapy registry.

Inclusion and exclusion

Inclusion criteria for this study were female patient’s ≥ 18 year’s old, primary neoplasia of the breast, received anthracycline-based or taxane-based therapy, and completed ≥ 2 cycles of chemotherapy. Exclusion criteria for this study were patients with recurrent cancer, patients with the non-complete medical record, referral for treatment between facilities, changes of chemotherapy regimen during treatment, and death before completion of a chemotherapy regimen.

Data variables

Individual subject data were collected retrospectively from patient medical records and a chemotherapy registry. The following data were collected: patient’s age, ethnicity, tumour histology and molecular subtype, treatment modality, chemotherapy regimen, scheduled and administered date of chemotherapy, the reason for schedule modification, and date of death or date of last follow up. Age was grouped into categories (< 50 years old and ≥ 50 years old), while patient ethnicity was categorised into Malay and non-Malay.
to reflect the population distribution. Tumours (Stage I–IV) were staged according to the 6th edition of TNM classification by American Joint Committee on Cancer (AJCC) [15], while the molecular subtype of the tumour was categorised according to the presence of the oestrogen receptor (ER; positive or negative) and human epidermal growth factor receptor 2 (HER2; positive or negative). Information regarding treatment data consisted of treatment modality (adjuvant/neo-adjuvant/palliative) and type of chemotherapy used (anthracycline-based/taxane-based/anthracycline + taxane). The duration of the delay was the difference from the scheduled chemotherapy date to the administered date. The total length of the chemotherapy regimen was calculated from the first date to the last date of chemotherapy administration. Patients who completed chemotherapy during the expected chemotherapy timeline were categorised as ‘no schedule modification’, patients who had a longer-than-expected chemotherapy duration were categorised as ‘with schedule modification’, and patients who did not complete the expected number of cycles were categorised as ‘incomplete schedule’. The reason for schedule modification was categorised as medical or non-medical reasons and the respective length of the delay for either reason was also calculated. The medical reason was defined as rescheduling by a physician with clinical evidence, while a non-medical reason was defined as rescheduling without an underlying medical cause such as a request by the patient or an administrative cause. The cumulative duration of the delay was categorised into < 14 days or ≥ 14 days. Data on mortality were obtained from the national registry database by matching the patient’s identification number.

Statistical analysis

All categorical variables were presented as the number (n) and percentage (%). Survival analysis was performed using Kaplan–Meier analyses to estimate OS and the difference in the survival rate was compared using the Breslow test (Generalized Wilcoxon). Univariate analysis of a simple Cox regression was conducted to screen for all independent variables. The variable selection for the multivariate Cox proportional hazard regression model was obtained using backward selection and the stepwise method. The final model was presented with the adjusted HR with the 95% CI and its corresponding p value. For all tests, a two-tailed p-value of < 0.05 was considered to be statistically significant. All statistical analyses were performed using SPSS for Windows version 22.0 (SPSS Inc., Chicago, IL, USA).

Results

Among 171 patients who were included in the final analysis, 16.4% [28] of patients had no schedule modification, 69% (118) of patients had a schedule modification, and the remaining 14.6% [25] of patients had an incomplete schedule. As shown in Table 1, 143 (83.6%) patients had at least one schedule modification while 123 (71.9%) patients had at least one schedule modification for a medical reason. Most patients had a schedule modification for a combination of medical and non-medical reasons including 59 (50%) patients with a schedule modification and ten (40%) patients with an incomplete schedule.

Patients included in the analysis were expected to receive 1002 chemotherapy cycles but only 931 cycles were observed (Table 2). Among the 931 observed cycles, 201 cycles were postponed, which corresponded to a delay of 1554 days. As shown in Table 3, 69.6% (140) of cycle schedule modifications occurred for medical reasons while non-medical reason contributed to the remaining 30.4% (61) of schedule modifications. When the duration of the delay (in days) was compared, medical reasons contributed to 1320 (84.9%) of days delayed, with a median delay of 7 days (range, 7–14 days), while non-medical reasons contributed to the remaining 234 days delay, with a median delay of 2 days (range, 1–6 days). This study shows that there were multiple reasons for modifying the chemotherapy schedule, but 94% (189) of all cycle rescheduling happened because of constitutional symptoms (70), for non-medical reasons (61) and blood/bone marrow toxicity (58). Similarly, the combination of these three reasons contributed to 93.8% (1458) of days delayed. The most frequent reason for schedule modification was because of constitutional symptoms, which accounted for 70 (34.8%) cycles and 724 (46.6%) days delay. In this study, the criteria for constitutional symptoms included temperature ≥ 38.0 °C or absolute neutrophil count < 1.5 × 10⁹/l or fatigue (either reported by the patient or diagnosed by a physician).

The impact of the chemotherapy schedule modification on survival outcome was investigated using a Kaplan–Meyer analysis. The overall unadjusted survival was statistically significant (χ² [2] = 6.136, p = 0.047; Fig. 1). The OS was 75.0% for patients with no schedule modification, 59.3% for patients with a schedule modification, and 52.0% for patients with an incomplete schedule (Table 4). A pairwise comparison between the schedule groups indicated that there was a significant difference in survival between the no schedule modification and incomplete schedule groups (Table 4). When the impact of a 14-day delay on survival outcome was analysed, the overall unadjusted survival was also statistically significant (χ² [3] = 9.243, p = 0.026; Fig. 2). While OS for patient with no schedule modification and an
incomplete schedule remained identical, OS for patients with a schedule modification < 14 days was 67.3% and that of patients with schedule modification ≥ 14 days was 52.4% (Table 4). An additional pairwise comparison indicated a statistically significant difference in survival between no schedule modification, incomplete schedule, and schedule modification ≥ 14 days (Table 4).

A final multivariate Cox proportional hazard regression model for OS that was adjusted for cancer stage, molecular subtype, type of chemotherapy, treatment modality, and schedule modification was performed (Table 5). When compared to patients with no schedule modification, patients with schedule modification had a 2.34-times higher risk of death (HR 2.34, 95% CI 1.03–5.32; \( p = 0.043 \)) while patients with an incomplete schedule had a 3.44-times higher risk of death (HR 3.44; 95% CI 1.12–10.33; \( p = 0.026 \)). When the length of schedule modification was categorised into < 14 days and ≥ 14 days, and the risk of death was 2.56-times higher for patients with a schedule modification that had a ≥ 14-day delay (HR 2.56, 95% CI 1.10–5.99; \( p = 0.030 \)), while patients with an incomplete schedule had a 3.44-times higher risk of death (HR 3.44; 95% CI 1.32–9.03; \( p = 0.012 \)) compared to patients without a schedule modification.
Discussion

The chemotherapy schedule is commonly modified in clinical practice by delaying a chemotherapy dose to treat treatment-related complications because both the patient and physician anticipate a greater survival benefit by continuing the anti-cancer treatment given the treatment’s curative intent. Less than one-quarter of the patients received chemotherapy within the optimal time frame as recommended by the clinical trial protocol.

Chemotherapy regimen protocols recommend that the chemotherapy cycles be delayed until patients’ investigational values are acceptable for administration of chemotherapeutic agents [16–22]. Thus, chemotherapy sessions are frequently rescheduled by 7 days, such as at our facility along with other leading oncology facilities [23–26], to allow for enough time to recover from treatment toxicity and for administrative convenience. Schedule modifications are widely acceptable because only 0.4% of treatment-related deaths [27] have been recorded, even with a prevalence of up to 42–64.5% of schedule modification for medical reasons [4, 28–34].

The high of proportion schedule modification (83.6%) in our study was anticipated because non-medical schedule modification criterion were included. Generally, non-medical reasons are not reported because the duration (1–6 days) is considered to be too short to have any significant clinical impact [24, 26]. Similarly, even when the non-medical schedule modifications in our study group were higher compared to the European Organisation for Research and Treatment of Cancer (EORTC) Soft Tissue and Bone Sarcoma group audit report (30.3% vs. 21%) [33], non-medical reasons were not a significant predictor of OS ($p = 0.227$) in this study. A higher prevalence of schedule modification in our study may result from patients’ sociodemographic characteristics because several studies have documented patients originating from a low socioeconomic neighborhood or a household without a vehicle who required repeat visits for chemotherapy, which was an important issue that could have caused schedule modification [27, 35–38].

One of the main aims of this study was to evaluate the impact of the chemotherapy schedule modification on survival outcome. The clinical practice of modifying the chemotherapy schedule to treat chemotherapy complications has been reported to result in suboptimal outcomes, including suboptimal antitumor efficacy and reduced survival rates [39–43]. Chemotherapy schedule modification increased the duration between chemotherapy cycles, which consequently reduced the treatment’s dose intensity. Henderson et al. proposed that the anti-tumour activity of cytotoxic agents depends on the drug used and on the schedule of drug administration [44]. This observation was further demonstrated in a study by Bonadonna et al., which analysed 20 years of follow-up data for the relationship between the delivered dose and survival outcome [41]. The study reported a 52% OS rate in patients who received the full dose intensity compared to a 25% OS rate among patients who received sub-optimal dose intensity. Moreover, the 25% OS rate was identical in the control group that received no chemotherapy. Although there was no control group in our study, there was an almost identical OS of 52.4% for patients who completed chemotherapy with a schedule modification of ≥ 14 days compared with 52.0% for patients who did not finish chemotherapy. The above result suggested that administration of chemotherapy with a prolonged schedule does not provide a superior survival outcome compared with

Table 2  Expected and observed number of chemotherapy cycle

| Regime (required number of cycle, days) | No of patients (N = 171) | Expected number of cycle to complete regime (N = cycle; N = days) | Observed number of cycle (N = cycle;N = days) |
|---------------------------------------|--------------------------|------------------------------------------------------------------|---------------------------------------------|
| Antracycline based                     |                          |                                                                  |                                             |
| FEC$^a$ (6, 105)                       | 97                       | 582, 10185                                                        | 530, 8967                                   |
| EC$^b$ (4, 63)                         | 3                        | 12, 189                                                          | 12, 211                                     |
| AC$^c$ (4, 63)                         | 9                        | 36, 567                                                          | 36, 586                                     |
| Taxane based                          |                          |                                                                  |                                             |
| Docetaxel (6, 105)                     | 16                       | 96, 1680                                                         | 89, 1781                                    |
| Antracycline + Taxane                  |                          |                                                                  |                                             |
| FEC$^a$→ Docetaxel (6, 105)            | 46                       | 276, 4830                                                        | 264, 4690                                   |
| Total: 1002, 17451                     |                          | Total: 931, 16235                                                 |                                             |

FEC$^a$: 5-Fluorouracil + Epirubicin + Cyclophosphamide,  EC$^b$: Epirubicin + Cyclophosphamide,  AC$^c$: Doxorubicin + Cyclophosphamide.$ N^d$: cumulative length of cycle interval and length of delays
patients who did not finish chemotherapy treatment or who received no treatment. In clinical practice, prolonged delays to restrict toxicity should be weighed against the benefit of completing chemotherapy according to the schedule.

The Cox analysis of schedule modification showed that the negative prognostic impact of schedule modification was affected by the different lengths of the delay. We analysed delays < 7 days and did not find a statistically significant impact on patient outcome in our study. Similarly, Motzer et al. reported that a delay of < 7 day had no influence on event-free survival [24] and another study by Denduluri et al. showed that the same duration of delay among advanced breast cancer patients was not associated with mortality [26]. A delay duration that is < 7 days was too short to have any negative prognostic effect on the survival outcome. With an increased length of delay, we found statistically significant evidence that a delay of ≥ 14 days increased the hazard for death by 2.56-times (HR 2.56; 95% CI 1.10–5.99; \( p = 0.030 \)). Our results are consistent with findings by Seebacher et al., who reported that patients with a delay between 9 and 19 days had a 2.6-times higher hazard of death (HR 2.6; 95% CI 1.3–5.4; \( p = 0.0008 \)) [45]. Similarly another study by Chirivella et al. reported a 1.41-times higher hazard of death among patients with a delay ≥ 15 days (HR 1.41, 95% CI 1.04–1.90, \( p = 0.027 \)) [46]. This finding suggests that short delays (<7 days) may be acceptable because they may prevent serious toxicity for patients. Delays ≥ 7 days were strongly discouraged except in extraordinary life-threatening circumstances. Conversely, our results suggest that patients who had schedule modification of ≥ 14 days were more likely to have poorer survival.

Our clinical findings of a lower OS among patients with schedule modification were anticipated. The negative prognostic effect of schedule modification could be explained by the dose intensity (total amount of drug delivered over the total time course of treatment) that was received by the patient. Several studies have shown superior OS among

| Variables                        | Cycle disruption N = 201 | Days delay N = 1554 | Median(IQR) |
|----------------------------------|--------------------------|---------------------|-------------|
| **Age at chemotherapy, years**   |                          |                     |             |
| < 50                             | 70                       | 534                 | 7(2,9)      |
| ≥ 50                             | 131                      | 1020                | 7(3,11)     |
| **Ethnic**                       |                          |                     |             |
| Malay                            | 139                      | 1112                | 7(2,12)     |
| Non Malay                        | 62                       | 442                 | 7(2,8)      |
| **Tumour stage**                 |                          |                     |             |
| Stage I                          | 5                        | 30                  | 7(1,11)     |
| Stage II                         | 38                       | 277                 | 7(2,9)      |
| Stage III                        | 120                      | 875                 | 7(2,9)      |
| Stage IV                         | 38                       | 372                 | 7(5,15)     |
| **Molecular subtypes**           |                          |                     |             |
| ER + HER2-                       | 56                       | 435                 | 7(4,11)     |
| ER + HER2+                       | 53                       | 418                 | 7(3,9)      |
| ER- HER2+                        | 16                       | 105                 | 7(3,9)      |
| ER- HER2-                        | 36                       | 263                 | 7(2,10)     |
| Result unavailable               | 40                       | 333                 | 7(2,14)     |
| **Treatment modality**           |                          |                     |             |
| Adjuvant                         | 113                      | 894                 | 7(2,10)     |
| Neoadjuvant                      | 41                       | 333                 | 7(6,10)     |
| Palliative                       | 47                       | 327                 | 7(2,12)     |
| **Type of chemotherapy**         |                          |                     |             |
| Anthacycline based               | 129                      | 894                 | 7 (4,10)    |
| Taxane based                     | 29                       | 333                 | 7(1,11)     |
| Anthacycline + Taxane            | 43                       | 327                 | 7(1,13)     |
| **Criteria for rescheduling**    |                          |                     |             |
| Medical Reason                   | 140                      | 1320                | 7(7,14)     |
| Blood/Bone Marrow Toxicity       | 58                       | 500                 | 7(5,11)     |
| Febrile Neutropenia              | 3                        | 28                  | 7(7,7)      |
| Constitutional symptom           | 70                       | 724                 | 7(7,14)     |
| Gastrointestinal                 | 4                        | 18                  | 2(1,11)     |
| Dermatology                      | 5                        | 50                  | 12(3,17)    |
| Non-Medical reason               | 61                       | 234                 | 2(1,6)      |
| Social                           | 47                       | 180                 | 2(1,6)      |
| Administrative                   | 14                       | 54                  | 2(1,6)      |

**Schedule modification**

|                                |                           |                     |             |
|                                | No schedule modification  | –                   | –           |
|                                | With schedule modification| 177                 | 1354        | 7(2,10)    |
|                                | Incomplete schedule       | 24                  | 200         | 7 (3,12)   |

Fig. 1 Kaplan-Meier survival function curve for schedule modification
patients receiving chemotherapeutic agents with a conventional dose intensity compared with a reduced dose intensity. These included studies by Arriagada et al. [47] and Lepage et al. [43] who reported a lower 2-year survival rate between patients who received the optimum dose compared to patients who received a reduced dose (43% vs. 26%, \( p = 0.02 \); and 72% vs. 61%, \( p = 0.02 \), respectively), and a study by Kaye et al. [48] with a follow-up period of 4 years also observed a lower OS in the optimum dose compared to the reduced dose group (32% vs. 27%, \( p =0.04 \)). Additionally, analysis of data from 1224 patients in three trials performed by the Radiation Therapy Oncology Group showed a reduction in the long-term survival rates in patients with non-resectable non-small-cell lung cancer as a result of unscheduled interruptions in treatment [49]. The above findings suggest that the established survival benefit of chemotherapy

### Table 4: Overall survival according to characteristic of patients included in study

| Demographic and clinical characteristics | Total (N=171) | Overall survival (%) | \( P \) Overall (Breslow) |
|------------------------------------------|--------------|----------------------|--------------------------|
| Age at chemotherapy, years              |              |                      |                          |
| <50                                      | 57           | 71.9                 | 0.219                    |
| \( \geq 50 \)                             | 114          | 55.3                 |                          |
| Ethnic                                   |              |                      |                          |
| Malay                                    | 105          | 62.9                 | 0.853                    |
| Non-Malay                                | 66           | 57.6                 |                          |
| Tumour Stage                             |              |                      |                          |
| Stage I                                  | 6            | 100                  | <0.001                   |
| Stage II                                 | 32           | 74.3                 | Pairwise comparison 1-4**, 2-4**, 3-4** |
| Stage III                                | 95           | 71.0                 | 1-2 ns, 2-3 ns, 1-3 ns    |
| Stage IV                                 | 38           | 16.2                 |                          |
| Molecular subtypes                       |              |                      |                          |
| ER + HER2-                               | 55           | 72.7                 | 0.030                    |
| ER + HER2+                               | 41           | 46.3                 | Pairwise comparison 1-2*, 1-4*, 2-5*, 1-5 ns, 24 ns |
| ER- HER2+                                | 16           | 50.0                 |                          |
| ER- HER2-                                | 29           | 51.7                 |                          |
| Result unavailable                       | 30           | 73.3                 |                          |
| Treatment modality                       |              |                      |                          |
| Adjuvant                                 | 109          | 79.8                 | <0.001                   |
| Neoadjuvant                              | 34           | 38.2                 | Pairwise comparison 1-2**, 1-3**, 2-3* |
| Palliative                               | 28           | 14.3                 |                          |
| Type of chemotherapy                     |              |                      |                          |
| Antracycline based                       | 109          | 59.2                 | <0.001                   |
| Taxane based                             | 16           | 6.2                  | Pairwise comparison 1-2**, 1-3*, 2-3** |
| Antracycline + Taxane                    | 46           | 82.6                 |                          |
| Reason For Modification                  |              |                      |                          |
| No Modification                          | 70           | 66.2                 | 0.227                    |
| Medical                                  | 54           | 52.7                 |                          |
| Non-Medical                              | 20           | 81.0                 |                          |
| Both medical and non-medical             | 27           | 48.1                 |                          |
| Schedule modification                     |              |                      |                          |
| No schedule modification                 | 28           | 75.0                 | 0.047                    |
| With schedule modification               | 118          | 59.3                 | Pairwise comparison 1-2 ns, 1-3*, 2-3 ns |
| Incomplete schedule                      | 25           | 52.0                 |                          |
| 14 day Schedule modification             |              |                      |                          |
| No schedule modification                 | 28           | 75.0                 | 0.026                    |
| With schedule modification < 14 day      | 55           | 67.3                 | Pairwise comparison 1-3*, 1-4*, 2-4*, 2-3 ns, 3-4 ns |
| With schedule modification ≥ 14 day      | 63           | 52.4                 |                          |
| Incomplete schedule                      | 25           | 52.0                 |                          |

Pairwise comparisons *\( p < 0.05 \), **\( p < 0.001 \), ns- not significant
regimens could not be replicated in clinical practice because of nonconformity to the clinical trial protocol. These results and reports established the negative prognostic effect on OS if the chemotherapy schedule was modified.

Despite the important results in this retrospective analysis, it seems that the mortality rate is affected by factors other than just the chemotherapy schedule. Although schedule modification was a statistically significant prognostic factor, cancer stage (Stage III and IV), molecular subtype (ER + HER2 + and ER − HER2 −), and treatment modality (neo-adjuvant and palliative) were also statistically significant confounding factors (Table 5). To verify our results, prospective studies that adjust for cancer stage, molecular subtype, and treatment modality when evaluating the impact of the chemotherapy schedule on long-term outcomes are required.

**Conclusion**

Nonconformity to the chemotherapy schedule is common in clinical practice because of treatment complications, patients’ social schedule conflicts, and facility administrative
reasons. Cumulative delays of ≥ 14 days are likely to have negative prognostic effect on patient survival. Thus, the duration of the delays between cycles should be reduced whenever possible to achieve the maximum chemotherapeutic benefit.

Acknowledgements Our study group would like to thank Director General, Ministry of Health Malaysia for approval to publish this research, Clinical Research Centre (Biostatistics & Data Repository Sector), the National Institute of Health, Setia Alam for the data link-age service, and the National Registration Department (JPN) for their willingness to share their mortality records for research purposes.

Funding This study and manuscript were not funded.

Conflict of interest The authors declare that they have no conflict of interest.

References

1. Giordano SH, Lin Y-L, Kuo YF, Hortobagyi GN, Goodwin JS. Decline in the use of anthracyclines for breast cancer. J Clin Oncol. 2012;30(18):2232.
2. Group EBCTC. Comparisons between different polychemotherapy regimens for early breast cancer: meta-analyses of long-term outcome among 100 000 women in 123 randomised trials. The Lancet. 2012; 379(9814): 432–44.
3. Group EBCTC. Effects of chemotherapy and hormonal therapy for early breast cancer on recurrence and 15-year survival: an overview of the randomised trials. The Lancet. 2005; 365(9472): 1687–717.
4. Lyman GH, Dale DC, Crawford J. Incidence and predictors of low dose-intensity in adjuvant breast cancer chemotherapy: a nationwide study of community practices. J Clin Oncol. 2003;21(24):4524–31.
5. Wu Y, Aravind S, Ranganathan G, Martin A, Nalysnyk L. Anemia and thrombocytopenia in patients undergoing chemotherapy for solid tumors: a descriptive study of a large outpatient oncology practice database, 2000–2007. Clin Ther. 2009;31:2416–32.
6. Riccardi A, Pugliese P, Danova M, Brugnatelli S, Grasso D, Giordano M, et al. A phase II study of sequential 5-fluorouracil, epirubicin and cyclophosphamide (FEC) and paclitaxel in advanced breast cancer (Protocol PV BC 97/01). Br J Cancer. 2001;85(2):141–6.
7. Martin M, Villar A, Sole-Calvo A, Gonzalez R, Massuti B, Lizon J, et al. Doxorubicin in combination with fluorouracil and cyclophosphamide (i.v. FAC regimen, day 1, 21) versus methotrexate in combination with fluorouracil and cyclophosphamide (i.v. CMF regimen, day 1, 21) as adjuvant chemotherapy for operable breast cancer: a study by the GEICAM group. Ann Oncol. 2003;14(6):833–42.
8. Iwata H, Sato N, Masuda N, Nakamura S, Yamamoto N, Kuroi K, et al. Docetaxel followed by fluorouracil/epirubicin/cyclophosphamide as neoadjuvant chemotherapy for patients with primary breast cancer. Jpn J Clin Oncol. 2011;41(7):867–75.
9. Bonneterre J, Dieras V, Tubiana-Hulin M, Bougnot M, Bonneterre ME, Delozier T, et al. Phase II multicentre randomised study of docetaxel plus epirubicin vs 5-fluorouracil plus epirubicin and cyclophosphamide in metastatic breast cancer. Br J Cancer. 2004;91(8):1466–71.
10. Italian Multicentre Breast Study with E, Ambrosini G, Balli M, Garusi G, Demicheli R, Jirillo A, et al. Phase III randomized study of fluorouracil, epirubicin, and cyclophosphamide v fluorouracil, doxorubicin, and cyclophosphamide in advanced breast cancer: an Italian multicentre trial. J Clin Oncol Off J Am Soc Clin Oncol. 1988; 6(6): 976–82.
11. Buzdar AU, Suman VJ, Merc-Bernstam F, Leitch AM, Ellis MJ, Boughey JC, et al. Fluorouracil, epirubicin, and cyclophosphamide (FEC-75) followed by paclitaxel plus trastuzumab versus paclitaxel plus trastuzumab followed by FEC-75 plus trastuzumab as neoadjuvant treatment for patients with HER2-positive breast cancer (Z1041): a randomised, controlled, phase 3 trial. Lancet. 2013;14(13):1317–25.
12. Hryniuk W, Levine M. Analysis of dose intensity for adjuvant chemotherapy trials in stage II breast cancer. J Clin Oncol. 1986;4(8):1162–70.
13. Liutkauskiene S, Jancinskaite R, Jurenieni K, Grizas S, Malonyte R, Juozaityte E. Retrospective analysis of the impact of platinum dose reduction and chemotherapy delays on the outcomes of stage III ovarian cancer patients. BMC Cancer. 2015;15(1):105.
14. Budman DR, Berry DA, Cirrincione CT, Henderson IC, Wood WC, Weiss RB, et al. Dose and dose intensity as determinants of outcome in the adjuvant treatment of breast cancer. JNCI J Natl Cancer Inst. 1998;90(16):1205–11.
15. Edge SB, Compton CC. The American joint committee on cancer: the 7th edition of the AJCC cancer staging manual and the future of TNM. Ann Surg Oncol. 2010;17(6):1471–4.
16. Krigel RL, Palackdharry CS, Padavic K, Haas N, Kilpatrick D, Langer C, et al. Ifosfamide, carboplatin, and etoposide plus granulocyte-macrophage colony-stimulating factor: a phase I study with apparent activity in non-small-cell lung cancer. J Clin Oncol. 1994;12(6):1251–8.
17. Elias A, Ryan L, Aisner J, Antman KH, editors. Mesna, doxorubicin, ifosfamide, dacarbazine (MAID) regimen for adults with advanced sarcoma. In: Seminars in oncology; 1990 (Vol. 17, pp. 41–49).
18. Veldhuis G, Willemsse P, Beijnen J, Boonstra H, Piersma H, Van der Graaf W, et al. Paclitaxel, ifosfamide and cisplatin with granulocyte colony-stimulating factor or recombinant human interleukin 3 and granulocyte colony-stimulating factor in ovarian cancer: a feasibility study. Br J Cancer. 1997;75(5):703.
19. Schütte J, Mouridsen H, Stewart W, Santoro A, Van Oosterom A, Somers R, et al. Ifosfamide plus doxorubicin in previously untreated patients with advanced soft tissue sarcoma. Eur J Cancer Clin Oncol. 1990;26(5):558–61.
20. Fetting JH, Gray R, Fairclough DL, Smith TJ, Margolin KA, Citron ML, et al. Sixteen-week multidrug regimen versus cyclophosphamide, doxorubicin, and fluorouracil as adjuvant therapy for node-positive, receptor-negative breast cancer: an intergroup study. J Clin Oncol. 1998;16(7):2382–91.
21. Boni C, Cocconi G, Bisagni G, Ceci G, Peracchia G. Cisplatin and etoposide (VP-16) as a single regimen for small cell lung cancer a phase II trial. Cancer. 1989;63(4):638–42.
22. Keefe DM, Elting LS, Nguyen HT, Grunberg SM, Aprile G, Bonaventura A, et al. Risk and outcomes of chemotherapy-induced diarrhea (CID) among patients with colorectal cancer receiving multi-cycle chemotherapy. Cancer Chemother Pharmacol. 2014;74(4):675–80.
23. American Society of Clinical Oncology. Recommendations for the use of hematopoietic colony-stimulating factors: evidence-based, clinical practice guidelines. J Clin Oncol. 1994;12(11):2471–508.
24. Motzer RJ, Geller NL, Bosl GJ. The effect of a 7-day delay in chemotherapy cycles on complete response and event-free survival in good-risk disseminated germ cell tumor patients. Cancer. 1990;66(5):857–61.
25. Wu Y, Aravind S, Nalyshyk L, Ranganathan G. Dose delay amongst cancer patients undergoing chemotherapy. Am Soc Hematol. 2008.

26. Denduluri N, Lyman GH, Wang Y, Morrow PK, Barron R, Patt D, et al. Chemotherapy dose intensity and overall survival among patients with advanced breast or ovarian cancer. Clin Breast Cancer. 2018;18(5):380–6.

27. Stitzenberg KB, Sigurdson ER, Egleston BL, Starkey RB, Meropol NJ. Centralization of cancer surgery: implications for patient access to optimal care. J Clin Oncol. 2009;27(28):4671.

28. Schraa S, Frierichs K, Agterolf M, Hunting J, Los M, de Jong P. Relative dose intensity as a proxy measure of quality and prognosis in adjuvant chemotherapy for breast cancer in daily clinical practice. Eur J Cancer. 2017;79:152–7.

29. Lyman GH. Impact of chemotherapy dose intensity on cancer patient outcomes. J Natl Compr Canc Netw. 2009;7(1):99–108.

30. Griffin DA, Penprase B, Klamerus JF, editors. Relative dose intensity—improving treatment and outcomes in early-stage breast cancer: a retrospective study. In: Oncology nursing forum; 2012.

31. Faustino C, Afonso N, Sousa B, Santo JE, Rodrigues H. Relative dose intensity reduction in breast cancer adjuvant chemotherapy. AACR; 2009.

32. Egwuonwu O, Anyanwu S, Nwofor A. Default from neoadjuvant chemotherapy in premenopausal female breast cancer patients: what is to blame? Nigerian J Clin Pract. 2012;15(3):265–9.

33. Steward W, Vantongelen K, Verweij J, Thomas D, Van Oosterom A. Chemotherapy administration and data collection in an EORTC collaborative group—can we trust the results? Eur J Cancer. 1993;29(7):943–7.

34. Chang J. Chemotherapy dose reduction and delay in clinical practice: evaluating the risk to patient outcome in adjuvant chemotherapy for breast cancer. Eur J Cancer. 2000;36:11–4.

35. Scoggins JF, Fedorenko CR, Donahue SM, Buchwald D, Blough DK, Ramsey SD. Is distance to provider a barrier to care for medicaid patients with breast, colorectal, or lung cancer? J Rural Health. 2012;28(1):54–62.

36. Guidry JJ, Aday LA, Zhang D, Winn RJ. Transportation as a barrier to cancer treatment. Cancer Pract. 1997;5(6):361–6.

37. Salloum RG, Smith TJ, Jensen GA, Lafata JE. Factors associated with adherence to chemotherapy guidelines in patients with non-small cell lung cancer. Lung Cancer. 2012;75(2):253–60.

38. Liutkauskienė S, Grīzas S, Jurienienė K, Stupytė J, Statnickaite A, Juozaityte E. Retrospective analysis of the impact of anthracycline reduction and chemotherapy delays on the outcomes of early breast cancer molecular subtypes. BMC Cancer. 2018;18(1):453.

39. Wood WC, Budman DR, Korzun AH, Cooper MR, Younger J, Hart RD, et al. Dose and dose intensity of adjuvant chemotherapy for stage II, node-positive breast carcinoma. N Engl J Med. 1994;330(18):1253–9.

40. Savarese D, Hsieh CC, Stewart FM. Clinical impact of chemotherapy dose escalation in patients with hematologic malignancies and solid tumors. J Clin Oncol. 1997;15(8):2981–95.

41. Bonadonna G, Valagussa P, Moliterni A, Zambetti M, Brambilla C. Adjuvant cyclophosphamide, methotrexate, and fluorouracil in node-positive breast cancer—the results of 20 years of follow-up. N Engl J Med. 1995;332(14):901–6.

42. Hryniuk W, Bush H. The importance of dose intensity in chemotherapy of metastatic breast cancer. J Clin Oncol. 1984;2(11):1281–8.

43. Lepage E, Gisselbrecht C, Sebban C, Tilly H, Bosly A, et al. Prognostic significance of received relative dose intensity in non-Hodgkin’s lymphoma patients: application to LNH-87 protocol. Ann Oncol. 1993;4(8):651–6.

44. Henderson I, Hayes DF, Gelman R. Dose-response in the treatment of breast cancer: a critical review. J Clin Oncol. 1988;6(9):1501–15.

45. Seebacher V, Reinthaller A, Koelbl H, Concin N, Nehoda R, Polterauer S. The Impact of the Duration of Adjuvant Chemotherapy on Survival in Patients with Epithelial Ovarian Cancer - A Retrospective Study. PLoS One. 2017;12(1):e0169272-e.

46. Chirivel I, Bermejo B, Insa A, Perez-Fidalgo A, Magro A, Rosello S, et al. Optimal delivery of anthracycline-based chemotherapy in the adjuvant setting improves outcome of breast cancer patients. Breast Cancer Res Treat. 2009;114(3):479–84.

47. Arriagada R, Le Chevalier T, Pignon J-P, Riviere A, Mendonca F, Coll N, et al. Prognostic significance of received relative dose intensity in patients with limited small-cell lung cancer. J Clin Oncol. 1993;11(6):1501–52.

48. Kaye S, Paul J, Cassidy J, Lewis C, Duncan I, Gordon H, et al. Mature results of a randomized trial of two doses of cisplatin for the treatment of ovarian cancer. Scottish Gynecology Cancer Trials Group. Journal of clinical oncology. 1996;14(7):2113-9.

49. Cox JD, Pajak TF, Asbell S, Russell AH, Pederson J, Byhardt RW, et al. Interruptions of high-dose radiation therapy decrease longterm survival of favorable patients with unresectable non-small cell carcinoma of the lung: analysis of 1244 cases from 3 radiation therapy oncology group (RTOG) trials. Int J Radiat Oncol Biol Phys. 1999;47(3):493-8.

Publisher’s Note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.