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Concurrent sequencing of full-dose CMF chemotherapy and radiation therapy in early breast cancer has no effect on treatment delivery☆

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Abstract

With the increasing use of breast-conserving therapy plus systemic chemotherapy for the treatment of early breast cancer, the optimal sequencing of radiation therapy and chemotherapy remains controversial. Sequencing of therapy may influence not only treatment delivery, but control rates, complications and cosmesis. The aim of this study was to evaluate whether concurrent sequencing of standard doses of CMF (cyclophosphamide, methotrexate and 5-fluorouracil) and adjuvant radiation therapy for early breast cancer impacted on optimum treatment delivery. As both an intravenous (i.v.) 3-week regimen and classic (standard) CMF were utilised in this study, both types of CMF were compared. The effect of sequencing on complications and treatment delays were also assessed. 116 patients treated with CMF chemotherapy and adjuvant tangent breast radiation were studied. 73 patients were treated prospectively with concurrent therapy and were retrospectively compared with a matched group of 40 patients treated with sequential or sandwich therapy. All patients had stage 1 or 2 cancers. There were no planned dose reductions introduced for either treatment modality. Concurrent sequencing had no impact on the ability to deliver optimum radiation or chemotherapy doses. There was no significant difference in acute Radiation Therapy Oncology Group (RTOG) skin reactions or complications between the two groups. Although small, there was a significant delay (1.32 days (0–15 versus 0.36 (0–7)) in the concurrent group ($P=0.03$) in the delivery of radiation therapy. Sequencing had no significant effect on haematological parameters. 'Standard' CMF had a more profound effect on treatment delivery than i.v. CMF (Radiation delay 2.2 days versus 0.26, $P=0.002$, % chemotherapy delivered 93% versus 99% $P=0.000004$). At a mean follow-up of 2.6 years, there was no difference in the cosmetic scores between the two groups. Both local and distant control rates were excellent. This study has shown that standard radiation therapy can be delivered safely concurrently with CMF chemotherapy. Whether this approach may lead to better control rates in the future needs further study.

Keywords: Radiation; Chemotherapy; Concurrent therapy; Complications; Control rates

1. Introduction

The optimal sequencing of chemotherapy and radiation therapy in early stage breast cancer remains controversial. Either 'standard' or 'modified 3-weekly intravenous (i.v.)' CMF (cyclophosphamide, methotrexate, 5-fluorouracil) chemotherapy are well-accepted adjuvant treatment regimens for early breast cancer, shown to improve outcome in randomised trials as well as in a meta-analysis [1]. Adjuvant radiation to the breast after breast-conserving surgery significantly reduces the risk of an inbreast recurrence [2]. However, retrospective studies have suggested an increase in local recurrence rates when radiation therapy is delayed to deliver a full regimen of chemotherapy and an increase in distant failure if chemotherapy is delayed to deliver radiation therapy [3–9]. Concurrent sequencing of CMF chemotherapy is an attractive option for patients in that it shortens

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overall treatment times by up to two months and avoids treatment delays. However, the toxicity with this approach with regard to optimum treatment delivery has not been well described. It is also unclear whether the two accepted CMF regimens might influence treatment delivery, independent of radiation sequencing. There is little published information on concurrent treatment delivery using both standardised radiation fields and chemotherapy dose reduction rules. The aim of this study was to evaluate whether concurrent sequencing of standard doses of both CMF chemotherapy and radiation therapy influence the ability to deliver optimum doses of both treatment modalities. As both an i.v. 3-week regimen and classic (standard) CMF were utilised in this study, both types of CMF were also compared. The effect of concurrent sequencing on treatment delays and acute complications were also assessed. Both standardised radiation fields and chemotherapy dose reductions were used in this study.

2. Patients and methods

Between 1986 and 1998, 116 patients were treated with CMF chemotherapy and adjuvant tangent breast irradiation for early breast cancer at a single institution. 73 patients were treated prospectively with concurrent full dose CMF chemotherapy and concurrent radiation at standard dose per fraction. These patients were retrospectively compared with a matched group of 40 patients treated with sequential or sandwich therapy. All patients had stage 1 or 2 disease and all were treated with tangent breast radiation without nodal treatment. The characteristics of the two groups are outlined in Table 1. The mean age of the concurrent group (group 1) was 49 years (range 29–71 years) compared with 49 years (range 31–72 years) for the sequential group. All patients were treated with breast-conserving therapy. Adjuvant radiation was delivered by tangent 6MV photon beams with the dose prescribed to either the National Surgical Adjuvant Breast and Bowel Project (NSABP) point or to the isocentre. All patients received a boost to the tumour bed by direct *en-fosse* electron beam therapy. The doses prescribed and the dose per fraction in the two cohorts are outlined in Table 2. Standard radiation doses were delivered to group 1 without planned dose reductions.

Type of CMF chemotherapy 'standard' versus i.v., was according to the oncologist's preference. The standard regimen consisted of cyclophosphamide 100 mg/m^2 orally (p.o.) days 1–14, methotrexate 40 mg/m^2 i.v. days 1 and 8 and 5-fluorouracil 600 mg/m^2 days 1 and 8 repeated every 28 days for six cycles. The i.v. regimen consisted of cyclophosphamide 600 mg/m^2 i.v., methotrexate 40 mg/m^2 i.v. and 5-fluorouracil 600 mg/m^2 i.v. repeated every 21 days for six to eight cycles. 43 patients were treated with 'standard' CMF while 73 patients were treated with the i.v. regimen. As with the radiation therapy, there was no planned dose reductions or removal of agents introduced for the concurrent group. The chemotherapy details are also outlined in Table 3. Other patient characteristics assessed included: number of nodes removed/number of positive nodes, breast separation, co-morbid conditions and number of courses of chemotherapy planned (Table 1). Breast separation was used as a surrogate for breast size as a large breast size is associated with a higher risk of

Table 1
Patients' characteristics

	Concurrent	Sequential	
Age (years)	49 (29–71)	49 (31–72)	$P=0.99$
Stage			
T1bN0	17	6	$P=0.13$
T1cN0	30	12	
T2N0	17	11	
T1/T2 N1	9	11	
No. of nodes removed	17 (8–31)	16.4 (5–31)	$P=0.665$
Co-morbid factors	16.4%	20%	
Breast separation (cm)	18.2 (12–29)	19.2 (13–32.5)	

Table 2
Delivery of radiation therapy

	Concurrent	Sequential	
Dose (Gy)	59.58 (50–63)	59.42 (50–64)	$P=0.09$
Dose per fraction			
2 Gy	31	24	
1.8 Gy	42	16	
% Delivered	100%	100%	$P=0.92$
Radiation delay (days)	1.32 (0–15)	0.36 (0–7)	$P=0.03$
RTOG acute skin reaction			
0	0	1	$P=0.81$
1	7	5	
2	37	20	
3	29	14	

RTOG, Radiation Therapy Oncology Group.

Table 3
Delivery of chemotherapy

	Concurrent	Sequential	
Type CMF			
Standard	28	15	
Intravenous (i.v.)	45	25	
No. courses	6 (4–10)	6.2 (6–10)	$P=0.168$
% Delivered	97% (60–100)	97% (75–100)	$P=0.927$
Delay (days)	8.4 (0–35)	7.3 (0–39)	$P=0.367$
Nadir granulocyte count (10^9 cell/l)	1207 (180–2706)	1300 (216–3900)	$P=0.416$
Nadir platelet count (10^9 cell/l)	183 (38–392)	187 (112–288)	$P=0.871$
Acute complications	2	1	

CMF, cyclophosphamide, methotrexate, 5-fluorouracil.

radiation-induced acute skin reactions. Premorbid conditions such as diabetes and hypertension were recorded as these conditions may influence the tolerance to treatment.

Patients in the concurrent group were assessed weekly during radiation therapy by two investigators and the grade of acute radiation reaction according to the Radiation Therapy Oncology Group (RTOG) guidelines was scored. The highest score recorded during the course of radiation therapy was subsequently assessed. Any delay in radiation treatment due to the toxicity of treatment, whether from skin reactions or haematological parameters, was also recorded. The charts of group 2 were reviewed and similar parameters assessed. As is standard in this institution, the radiation acute reaction score is assessed weekly during therapy and any delay in radiation therapy was recorded (defined as any interruption in radiation treatment introduced because of toxicity and measured in days).

Similarly the delivery of the chemotherapy dose was according to standard calculations based on Body Surface Area (BSA) and ideal doses as outlined above. The percentage dose of planned chemotherapy actually delivered when compared with ideal doses and number of planned courses delivered were assessed. Nadir neutrophil, lymphocyte and platelet counts were recorded before each course of chemotherapy for 'i.v. CMF' and between courses for 'standard' CMF. The lowest nadir count recorded for each haematological parameter was assessed. Any delay in chemotherapy delivery because of toxicity was also recorded (defined as a greater than 7-day prolongation in chemotherapy delivery).

The Mann–Whitney test was used to determine whether there was an imbalance in prognostic variables between the two groups. Differences in nadir counts were assessed by multiple regression analysis. For radiation delay, chemotherapy delay, number of courses of chemotherapy delivered and percentage of planned chemotherapy delivered, the proportional odds polytomous regression analysis was used and continuous variables such as radiation delay and chemotherapy delay were made categorical. A multivariate analysis was performed on variables to assess their effect on overall outcome.

3. Results

Differences in potential prognostic variables between the two groups were assessed by the Mann–Whitney test. Parameters assessed were age, stage, number of nodes removed, co-morbid conditions (diabetes and hypertension) and breast separation. There was no significant difference between the two groups in these variables (Table 1).

3.1. Delivery of radiation therapy

As previously mentioned, there was no planned dose reduction in radiation therapy introduced for the concurrent group. Radiation therapy was generally sequenced after the second course of CMF chemotherapy in the concurrent group and after the final course of chemotherapy in the sequential group. Sequencing had no effect on the ability to deliver the planned radiation therapy. Table 2 outlines the doses and fractionation delivered in each group. 100% of the planned dose was delivered in each group. Table 2 also outlines the maximum acute RTOG skin reactions seen during the course of radiation treatment. There were a slightly higher percentage of grade 3 reactions in the concurrent group, but the differences did not reach statistical significance in the polytomous regression analysis ($P = 0.81$). More patients in the concurrent group needed a break during the radiation, mainly due to either skin or haematological toxicities. Although the difference was small between the two groups (1.32 days; range 0–15 days and 0.36; range 0–7 days), this difference was statistically significant ($P = 0.03$). The type of CMF chemotherapy had a more profound effect on radiation treatment delivery than concurrent sequencing. Although the prescribed dose was delivered, there was a significantly longer delay in delivery with the 'standard' regimen than the i.v. regimen (2.2 days versus 0.26 days; $P = 0.002$) because of haematological toxicity.

3.2. Delivery of chemotherapy

Patients were treated with either 'standard' CMF chemotherapy every 4 weeks or i.v. CMF chemotherapy every 3 weeks according to the physician's preference. 28 patients in the concurrent group were treated with 'standard' CMF compared with 15 in the sequential group, while 45 patients in the concurrent group were treated with i.v.. CMF compared with 25 in the sequential group. The type of chemotherapy either 'standard' or 'i.v.' had a more profound effect on treatment delivery than sequencing did. 'Standard' chemotherapy resulted in a significantly lower percentage of planned chemotherapy delivery (93% versus 99%; $P = 0.000004$). However, there was no effect on the delay in the delivery of chemotherapy. Sequencing of therapy had no effect on the ability to deliver optimum chemotherapy or on the delay in the delivery of chemotherapy due to enhanced toxicity (Table 3).

3.3. Toxicity

Sequencing had no significant effect on haematological parameters. Although the nadir granulocyte counts were lower in the concurrent group (1207; range 180–2706) than in the sequential group (1300; range 216–3900),

this difference was not significant ($P = 0.416$). There was no effect of sequencing on the nadir platelet counts (Table 3). Type of CMF resulted in lower platelet nadirs than granulocyte nadirs, which did affect chemotherapy delivery as mentioned above. Other than acute skin reactions, there were two acute complications in the concurrent group (pericarditis and cellulitis) and one in the sequential group (congestive cardiac failure).

3.4. Cosmesis

The cosmetic score was evaluated every 6 months by two independent observers for the concurrent group. A standardised score 1–4 was used for the following parameters: retraction, fibrosis, pigmentation and oedema. An overall score was then recorded (excellent, good, satisfactory and poor) for each patient. As a similar cosmetic score was available in the charts for the sequential group, the two groups were compared. At a mean follow-up of 2.4 years in the concurrent group and 2.9 years in the sequential group, there was no significant difference in the cosmetic score between the two groups. The percentage of patients with an excellent, good, satisfactory and poor cosmetic score was 73, 22, 3 and 2% in the concurrent group and 70, 30, 0 and 0% in the sequential group, respectively.

3.5. Control rates

Both local and distant control rates were excellent; few patients recurred in either group. There was one distant failure and no local failures in the concurrent group compared with four distant and one local failure in the sequential group.

4. Discussion

The optimal sequencing of radiation therapy and chemotherapy in early breast cancer remains controversial. Although a concurrent sequencing approach is attractive, there are a number of concerns with this approach related to treatment delivery and complications. A number of studies have reported a deleterious effect of radiation therapy on the ability to deliver optimum doses of chemotherapy and have suggested this may affect treatment outcome [7,8,10,11]. This study has shown that the type of CMF chemotherapy influences treatment delivery more significantly than concurrent sequencing. Glick and colleagues from the University of Pennsylvania have reported on a trial integrating concurrent chemotherapy using CF (i.v. regimen) with radiation therapy followed by six cycles of CMFP [12]. This study reported no effect of radiotherapy on either CF or CMFP delivery, with 89% of the planned chemotherapy dose delivered. Another German study prospectively treated 45 patients with modified CMF chemotherapy concurrent with chest wall and regional nodal radiation. No severe side-effects were noted and 5-year survival rates of 83% were promising [13]. The lack of an influence of radiation delivery on treatment outcome may be due to the chemotherapy regimen chosen rather than the sequencing of radiation therapy. In our study, patients were treated by breast tangents without regional node radiation and chemotherapy dose reductions were based on granulocyte nadirs. Despite concurrent therapy and the use of standard doses, there was no influence of sequencing on either the nadir granulocyte counts or on the percentage of planned chemotherapy actually delivered.

Altering the schedule of CMF from the ‘standard’ CMF to the ‘modified’ i.v. CMF has compromised outcome in advanced breast cancer [11,14]. An European Organization for Research and Treatment of Cancer (EORTC) phase 3 trial reported a significantly reduced response rate with i.v. CMF compared with ‘standard’ CMF (29% versus 48%) [15]. Survival was also longer in the standard CMF group [15]. The reason for this difference is unclear; our toxicity data would suggest that perhaps the ‘standard regimen’ is a more intensive regimen than i.v. CMF. I.v. CMF has not been compared head-to-head with ‘standard’ CMF in the adjuvant setting. However, a randomised trial in node-negative patients comparing i.v. CMF with surgery found a significant improvement in disease-free survival at 8 years in the chemotherapy arm [16]. There was no difference in outcome between the ‘standard’ CMF group and i.v. CMF group as adjuvant therapy in this study. Small numbers and low stage may have influenced this finding. Interestingly, despite having a lower overall percentage delivery with ‘standard’ CMF than i.v. CMF (93% versus 99%), this did not influence patient outcome in this study.

Controversy also exists regarding whether delaying radiation therapy until after chemotherapy affects the local control rates [3,4,17]. A number of retrospective studies have shown an increased risk of local recurrence when radiation is delayed to administer chemotherapy. Recht and colleagues reported an actuarial 5-year local failure rate of 4% in patients receiving radiation prior to chemotherapy, 6–8% in patients treated with either concurrent or sandwich therapy and 41% in patients who received all of their chemotherapy before radiotherapy. The failure rate was 5% for radiation within 16 weeks after surgery and 35% when greater than 16 weeks [3]. A randomised study from the same group initially reported a higher risk of local recurrence with delayed radiation therapy of 16 weeks, but this was not confirmed with a longer follow-up. A retrospective review of the International Breast Cancer Group randomised studies, however, did not find an increased risk of local recurrence when delaying radiation for up to 7

months [17]. Concurrent sequencing resulted in a small, but significant, delay in the delivery of radiation therapy in this study, although optimum doses were achieved. Despite this small delay, the local control rates in our study were excellent, with the only local recurrence occurring in the sequential group. Whether concurrent sequencing of therapy will result in an improved local control from the potential additive effect of the two modalities will await further follow-up and studies.

A concern with concurrent therapy involves the potential effect of sequencing on complications and cosmetic outcome. We did not find an increased risk of acute complications with concurrent sequencing in this study. Clinical pneumonitis was not seen in either group. The potential effect on the cosmetic score of concurrent sequencing is an important question in view of the patient population. There are conflicting reports in the literature on this topic [18,19]. Abner and colleagues reported a significant deleterious effect of concurrent sequencing on the cosmetic outcome of 50 patients evaluated in a retrospective fashion [20]. It is unclear from this study whether other potential factors that may impact on cosmetic outcome, such as breast size or co-morbid conditions were controlled for. In contrast a study from Markiewicz and colleagues found no effect of concurrent sequencing on cosmesis [19]. Although follow-up is relatively short, this study also found no effect of sequencing on the cosmetic outcome. Differences in cosmesis between studies is hard to evaluate as it is difficult to control for variables such as tumour site, surgical technique, breast size, radiation boost and co-morbid conditions.

5. Conclusions

This study has confirmed that standard radiation therapy and CMF chemotherapy can be safely delivered concurrently in well-selected patients (without regional node radiation). Type of CMF rather than sequencing significantly impacted on both the radiation and chemotherapy delivery. Despite this finding, control rates were excellent.

Concurrent sequencing has the advantage of shortening treatment times by up to 2 months for patients, while avoiding treatment delays. Whether optimally sequencing chemotherapy and radiation therapy as in the concurrent group may in time improve outcome will await further study.

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