Prognostication and treatment decision-making in early breast cancer

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7

Acute toxicity of concurrent adjuvant radiotherapy and chemotherapy (CMF or AC) in breast cancer: a prospective, comparative, non randomised study.

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ABSTRACT

Background: The concurrent administration of adjuvant chemotherapy and radiotherapy in breast cancer treatment might lead to an increased incidence of side effects.

Methods: In this prospective, non-randomised, comparative study the acute toxicity of radiotherapy alone (RT) and radiotherapy concurrent with doxorubicin-cyclophosphamide (AC/RT) and radiotherapy concurrent with cyclophosphamide-methotrexate-5-fluorouracil (CMF/RT) was compared. We used the Common Toxicity Criteria (CTC) to score the level of acute toxicity before, during and 6 months after the completion of the period of irradiation. The number of hospital admissions as well as the compliance of chemotherapy, were noted.

Results: We observed that patients treated with AC/RT and CMF/RT had significant higher incidences of (high-grade) skin-toxicity, oesophagitis, dyspnoea, malaise, anorexia, nausea and hospital admission compared with those treated with RT only. The target-volume of radiotherapy was the main predictor of (high-grade) acute skin toxicity and oesophagitis. AC/RT was associated with significant more (high-grade) skin toxicity than CMF/RT. The dose of chemotherapy was reduced to less than 85% of the planned dose in 11% of patients, 17% of patients treated with concurrent chemotherapy and radiotherapy needed admission to hospital .

Conclusions: From the results of our study, we conclude that the concurrent administration of adjuvant chemotherapy and radiotherapy leads to an unacceptably high level of acute toxicity.

INTRODUCTION

The optimal sequence of radiotherapy and adjuvant chemotherapy in breast cancer patients is not clearly defined. The delivery of both regimens can be planned sequentially (chemotherapy administered before or after radiotherapy), concurrently (chemotherapy and radiotherapy given simultaneously), or alternating (radiotherapy administered in the midst of the chemotherapy courses, commonly referred to as “sandwich” therapy).

In order to limit the side-effects experienced, most centres deliver radiotherapy and adjuvant chemotherapy sequentially. However, a delay in the delivery of radiotherapy[1-5] or systemic therapy[6] might have a negative effect on treatment outcome. In an evaluation of data from a number of trials from the National Surgical Adjuvant Breast and Bowel Project (NSABP), in which concurrent treatment was compared with sequential treatment, concurrent treatment was associated with a decreased incidence of ipsilateral breast recurrences after breast conserving therapy (BCT).[7] However, it is known that the concurrent administration of radiotherapy and chemotherapy leads to an increased incidence of side effects,[8-15] that the chemotherapy regimens used in these NSABP trials are considered substandard today and that the degree of toxicity of combined chemotherapy and radiotherapy also depends on the type of cytotoxic drugs used.[16,17] The increased level of toxicity, caused by the concurrent administration of chemo- and radiotherapy, might compromise optimal dose delivery, with respect to both radiotherapy and chemotherapy treatments.[15,18] This might have negative influence on treatment outcome. Hence, the balance between gain in disease control versus the side-effects might be different with the current chemotherapy and radiotherapy regimens.

In this prospective, comparative, non-randomised study, the acute toxicity of radiotherapy concurrent with cyclophosphamide-methotrexate-fluorouracil (CMF/RT) was compared with that of radiotherapy concurrent with (epi-)doxorubicin-cyclophosphamide (AC/RT). A third group treated with radiotherapy only (RT) was added.

Table 7.1. Patient-, tumour- and treatment-characteristics.

	AC/RT	CMF/RT	RT
Number of patients	61	51	42
Median age in years (range)	47 (27-64)	43 (28-56)	53 (37-74)
Interval between date of surgery and start of radiotherapy in days (range)	57 (35-119)	58 (31-103)	53 (31-98)
Interval between date of surgery and start of chemotherapy in days (range)	35 (15-91)	29 (9-92)	
Primary surgical treatment			
Breast conserving therapy	34 (56%)	37 (73%)	36 (86%)
Modified radical mastectomy	27 (44%)	14 (27%)	6 (14%)
Tumour size			
≤ 20 mm	18 (30%)	25 (49%)	28 (67%)
21 – 50 mm	36 (59%)	24 (47%)	13 (31%)
> 50 mm	7 (11%)	2 (4%)	1 (2%)
Axillary lymph node status			
Tumour negative	4 (7%)	3 (6%)	27 (64%)
Tumour positive	57 (93%)	48 (94%)	15 (36%)
Target-volume radiation therapy			
Local	25 (41%)	28 (55%)	30 (71%)
Loco-regional	36 (59%)	23 (45%)	12 (29%)

AC, doxorubicin-cyclophosphamide; CMF, cyclophosphamide-methotrexate-fluorouracil; RT, radiotherapy.

MATERIAL AND METHODS

Patients

Between January 1996 and August 1999, all eligible patients referred to the department of radiotherapy at the University Medical Centre Utrecht (UMC Utrecht) were asked to participate in this prospective, comparative study. Informed consent was obtained from 154 patients. Patients were eligible if they were referred for RT or chemotherapy (CT)/RT, both after BCT and modified radical mastectomy (MRM). 112 patients received CT/RT; 61 patients were treated with AC/RT and 51 with CMF/RT. 42 patients treated with RT only were studied as controls. The choice between AC and CMF was made by the treating medical oncologist and was based on personal preference. Table 8.1 depicts the patient and treatment characteristics for the 3 patient groups. The AC/RT and CMF/RT groups were not fully balanced, specifically with respect to tumour and treatment characteristics . However, these differences were not statistically significant ($P>0.05$). The differences in patient-, tumour- and treatment characteristics between the CT/RT and RT groups can be explained by the treatment protocols used. In premenopausal patients, chemotherapy was given in the presence of axillary lymph node metastases. Since patients in the CT/RT groups were mostly premenopausal, we preferably included patients less than 50 years of age in the RT group. As a consequence, most patients included in the RT only group were axillary lymph node-negative. The higher rate of patients treated with BCT and local radiotherapy in the RT group can be explained by the fact that local radiotherapy is part of BCT. Radiation therapy of the breast (including a boost dose) was an integral part of the BCT. Patients treated with MRM were referred for radiotherapy based on characteristics of either the primary tumour and/or the axillary lymph node status. In these patients, adjuvant systemic therapy was indicated in most cases.

Radiotherapy

Radiation therapy was administered at the Department of Radiotherapy at the UMC Utrecht. After lumpectomy and axillary dissection, radiotherapy (whole breast irradiation (WBI) and a boost dose) was indicated. Thoracic wall irradiation (TWI) after MRM was administered when resection margins were found to be tumour-positive or when skin involvement was assessed by the pathologist. Regional radiotherapy encompassing the axillary, infraclavicular, supraclavicular and parasternal lymph node areas, was added in the presence of 4 or more positive axillary lymph node metastases; tumour involvement of the apical axillary lymph node; extranodal tumour growth; or when skin involvement was assessed by the pathologist. WBI, as well as TWI, were administered using opposed tangential photon fields on a 6 or 10 MV linear accelerator to a dose of 50 Gy at 2 Gy per fraction. In case of WBI, a boost dose of 14-16 Gy (tumour free resection margins) or 20 Gy (focally tumour positive resection margins) was given using either photon wedge fields or electrons. The dose was specified at the isocentre, according to the guidelines of the International Commision on Radiation Units and Measurements (ICRU) report 50.[19] In all cases of TWI, tissue equivalent material was applied on the skin to ensure a 100% skin dose. The thoracic wall, as well as the axillary, infraclavicular, supraclavicular and parasternal lymph node areas were treated using a technique described earlier.[20] A dose of 50 Gy was given. With regard to the parasternal field, an anterior-posterior field was given. Thirteen fractions were administered with photons (encompassing the oesophagus) and 12 fractions with electrons. In 2 patients, who required regional radiotherapy, it was possible to include the parasternal lymph node chain within the breast tangential fields. 7 patients who were referred for local radiotherapy after breast-conserving tumorectomy participated in the European Organization for Research and Treatment of Cancer (EORTC) 10925/22922 trial (parasternal/medial supraclavicular radiotherapy versus none) and were treated with a parasternal field and a medial supraclavicular field in addition to their breast tangential fields.

The median interval between the date of surgery and the start of radiotherapy was 56 days (range 31-119 days). No difference in duration of the duration of interval period was noted between chemotherapy-patients and controls.

Chemotherapy

During the accrual period of this study (1996-1999), the medical oncologists had their own preference with regard to prescribing either AC or CMF as adjuvant systemic treatment. However, a change was observed over the years. In 1996, two thirds of the patients who required chemotherapy received CMF, whilst in 1998 two thirds received AC. The drugs were administered according to the following doses and schedules: AC: doxorubicin - 60 mg per square meter of body-surface area intravenously (i.v.) on day 1; cyclophosphamide - 600 mg per square meter i.v. on day 1; cycles were repeated every 21 days for a total of four cycles. CMF: cyclophosphamide - 100 mg per square meter orally for 14 days, starting on day 1; methotrexate – 40 mg per square meter i.v. on days 1 and 8; 5-fluorouracil – 600 mg per square meter i.v. on days 1 and 8; cycles were repeated every 28 days for a total of six cycles. Depending on the level of haematological toxicity (leucocytes $<3.0x10^9$, granulocytes $<1.5x10^9$ or thrombocytes $<50x10^9$), the medical oncologist decided to reduce chemotherapy doses or expel deliverance. The median interval between the date of surgery and start of chemotherapy was 35 days (range 15-91 days) for AC/RT patients and 29 days (range 9-92 days) for CMF/RT patients. Five percent of AC/RT patients received the first cycle of chemotherapy during radiotherapy, 49% received one cycle before start of radiotherapy, 39% two cycles and 7% three cycles. Eight percent of CMF/RT patients received their first cycle of chemotherapy during radiotherapy, 47% received one cycle before start of radiotherapy, 41% two cycles and 4% three cycles. Planned and delivered chemotherapy doses were calculated in mg per meter squared per week. Dose reduction was calculated by subtracting the delivered dose divided by the planned dose from one.

Table 7.2. Common Toxicity Criteria.

Toxicity	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4
Skin	None or no change	Scattered macular or popular eruption or erythema that is asymptomatic	Scattered macular or popular eruption or erythema with pruritis or other associated symptoms	Generalized symptomatic macular, popular or vesicular eruption	Exfoliative dermatitis or ulcerating dermatitis
Oesophagitis / dysphagia	None	Painless ulcers, erythema, or mild soreness or dysphagia	Painful erythema, oedema, or ulcers, or moderate dysphagia but can eat without narcotics	Cannot eat solids, or requires narcotics to eat	Requires parenteral or enteral support or complete obstruction or perforation
Cough	No change	Mild, relieved by NPM meds	Requires narcotic antitussive	Uncontrolled cough	
Dyspnea	None or no change	Asymptomatic with abnormality in pulmonary function tests	Dyspnea on significant exertion	Dyspnea at normal level of activity	Dyspnea at rest
Radiation pneumonitis	None	Radiographic changes, no steroids needed	Steroids required	Oxygen required	Assisted ventilation required
Malaise	None	Mild, able to continue normal activities	Impaired normal daily activity or bedrest <50% of waking h	In bed or chair 50% of waking h	Bedridden or unable to care for self
Anorexia	None	Mild	Moderate	Severe	Life-threatening
Nausea	None	Able to eat reasonable intake	Intake significantly decreased but can eat	No significant intake	
Vomiting	None	Once in 24 h	2–5 x in 24 h	6–10 x in 24 h	>10 episodes in 24 h, or requiring i.v. support
Fever (in absence of infection)	None	37,1–38,0 ºC	38,1–40,0 ºC	>40,0 ºC <24 h	>40,0 ºC >24 h or fever with hypotension

meds, medicines; h, hours; i.v., intravenous; NPM, non prescription medication.

Side effects

Toxicity parameters were scored using the Common Toxicity Criteria (CTC) as developed by the National Cancer Institute (NCI).[21] In the present study toxicity parameters were prospectively scored by the treating radiation oncologist before the start of radiotherapy, every two weeks during radiotherapy, and 3 weeks, 6 weeks, 3 months and 6 months after the completion of radiotherapy. Items scored were the level of skin-toxicity, the severity of symptoms like oesophagitis/ dysphagia, cough, dyspnoea, malaise, anorexia, nausea, vomiting, and fever (Table 8.2). When cough was scored as grade 2 or 3, or when dyspnoea was scored as grade 3 or 4, or in case of other pulmonary complaints, a chest X-ray was taken in order to evaluate the presence or absence of radiation pneumonitis. When skin toxicity grade 4 was scored, the desquamated skin surface area was measured in square centimetres. The maximum surface area of skin desquamation was noted. For all of the toxicity parameters, the maximum toxicity grade was taken. For all of the toxicity parameters, except for skin, toxicity grade 2 or higher was considered clinically relevant and therefore high-grade. For skin toxicity grade 3 or higher was considered clinically relevant and therefore defined as high-grade. The number of hospital admissions that took place during the follow-up period was registered. Dose reductions of chemotherapy to less than 85% of planned dose (in mg/m^2/week) were considered to be of clinical relevance.

Statistical analyses

Statistical analysis was carried out using the Statistical Package for the Social Sciences (SPSS) for Windows, release 9.0 (SPSS Inc.). Incidences of high-grade maximum toxicity were compared in univariate analyses using the Pearson Chi-square test. Incidences of high-grade toxicity (significant in univariate analysis), hospital admissions and clinically relevant dose reductions of chemotherapy were compared in logistic regression analysis. Independent variables included in the

Table 7.3. Incidences of maximum common toxicity criteria grade 2, 3 and 4 during follow-up.

Toxicity	AC/RT	CMF/RT		CT/RT	RT	
Number of patients	61	51		112	42	
Skin			§			‡
Grade 2	15 (25%)	20 (39%)		35 (31%)	22 (52%)	
Grade 3	0 (0%)	3 (6%)		3 (3%)	2 (5%)	
Grade 4	43 (70%)	21 (41%)		64 (57%)	9 (21%)	
Esophagitis / dysphagia			§			†
Grade 2	14 (23%)	7 (14%)		21 (19%)	2 (5%)	
Grade 3	8 (13%)	0 (0%)		8 (7%)	0 (0%)	
Grade 4	0 (0%)	2 (4%)		2 (2%)	0 (0%)	
Cough						
Grade 2	7 (11%)	4 (8%)		11 (10%)	2 (5%)	
Grade 3	0 (0%)	0 (0%)		0 (0%)	0 (0%)	
Grade 4	0 (0%)	0 (0%)		0 (0%)	0 (0%)	
Dyspnea						†
Grade 2	23 (38%)	18 (35%)		41 (37%)	5 (12%)	
Grade 3	3 (5%)	3 (6%)		6 (5%)	2 (5%)	
Grade 4	0 (0%)	1 (2%)		1 (1%)	0 (0%)	
Radiation pneumonitis						
Grade 2	3 (5%)	2 (4%)		5 (4%)	1 (2%)	
Grade 3	0 (0%)	0 (0%)		0 (0%)	0 (0%)	
Grade 4	0 (0%)	0 (0%)		0 (0%)	0 (0%)	
Malaise						‡
Grade 2	38 (62%)	31 (61%)		69 (62%)	17 (40%)	
Grade 3	15 (25%)	6 (12%)		21 (19%)	2 (5%)	
Grade 4	0 (0%)	0 (0%)		0 (0%)	0 (0%)	
Anorexia			§			‡
Grade 2	25 (41%)	10 (20%)		35 (31%)	1 (2%)	
Grade 3	6 (10%)	5 (10%)		11 (10%)	1 (2%)	
Grade 4	0 (0%)	0 (0%)		0 (0%)	0 (0%)	
Nausea			§			†
Grade 2	15 (25%)	6 (12%)		21 (19%)	1 (2%)	
Grade 3	3 (5%)	1 (2%)		4 (4%)	0 (0%)	
Grade 4	0 (0%)	0 (0%)		0 (0%)	0 (0%)	
Vomiting						§
Grade 2	8 (13%)	4 (8%)		12 (11%)	0 (0%)	
Grade 3	1 (2%)	0 (0%)		1 (1%)	0 (0%)	
Grade 4	0 (0%)	0 (0%)		0 (0%)	0 (0%)	
Fever						§
Grade 2	7 (11%)	5 (10%)		12 (11%)	0 (0%)	
Grade 3	0 (0%)	0 (0%)		0 (0%)	0 (0%)	
Grade 4	0 (0%)	0 (0%)		0 (0%)	0 (0%)	

AC, doxorubicin-cyclophosphamide; CMF, cyclophosphamide-methotrexate-fluorouracil; CT, chemotherapy; RT, radiotherapy. Incidences of maximum high-grade toxicities compared in bivariate analyses. § P<0.05; † P<0.01; ‡ P<0.001.

analysis were age, primary surgical therapy (MRM vs. BCT), target-volume of radiotherapy (local radiotherapy vs. loco-regional radiotherapy) and chemotherapy regimen (CT/RT vs. RT and CMF/RT vs. AC/RT). Since WBI was delivered after BCT only and TWI after MRM only, MRM vs. BCT could - in cases of acute skin toxicity - also be interpreted as TWI vs. WBI. T-stage or N-stage were not considered to be confounding factors, and we therefore decided not to include these variables in the multivariate analyses. The influence of the independent variables mentioned above on the duration of skin toxicity, oesophagitis/dysphagia and malaise was determined using Cox regression analysis. Their effect on the natural logarithm of the maximum area of skin desquamation was determined using linear regression analysis.

RESULTS

Incidences of maximum toxicity grades 2, 3 and 4 are presented in Table 8.3. Significantly more patients receiving CT/RT than patients receiving RT only experienced severe skin toxicity (60% vs. 26%), and moderate or severe esophagitis / dysphagia (28% vs. 5%), dyspnoea (43% vs. 17%), malaise (81% vs. 45%) anorexia (41% vs. 4%), nausea (22% vs. 2%), vomiting (12% vs. 0%) and fever (11% vs. 0%). When patients receiving AC/RT were compared with those receiving CMF/RT more high-grade skin-toxicity (70% vs. 47%) and moderate to high-grade toxicity of the oesophagus (36% vs. 18%) was observed for the AC/RT group. The intake of food was also significantly decreased (30% vs. 14%), and more patients experienced moderate to high (Grades 2 and 3) anorexia (51% vs. 29%).

The three study groups (AC/RT, CMF/RT and RT) were not fully balanced with respect to other potential risk factors for acute toxicity such as primary surgical treatment, radiotherapy regimen and age (Table 1). Hence, a logistic regression

Table 7.4. Multiple logistic regression analysis on incidences of high-grade toxicities.

	CT/RT vs. RT	AC vs. CMF	Loco–regional vs. local radiotherapy
	p-value O.R. (95% C.I.)	p-value O.R. (95% C.I.)	p-value O.R. (95% C.I.)
Skin	0.02 3.4 (1.2-9.5)	0.05 2.4 (1.0-5.8)	0.001 5.7 (2.1-15.5)
Oesophagitis / dysphagia	0.03 7.2 (1.2-43)	0.08 2.4 (0.90-6.1)	0.001 7.6 (2.2-26)
Dyspnoea	0.003 5.1 (1.7-15)	0.68 0.85 (0.39-1.9)	n.s.
Malaise	<0.001 7.1 (2.6-20)	0.11 2.3 (0.84-6.1	n.s.
Anorexia	0.001 13 (2.8-67)	0.06 2.1 (0.96-4.8)	n.s.
Nausea	0.03 12 (1.4-100)	0.06 2.6 (0.96-6.9)	n.s.

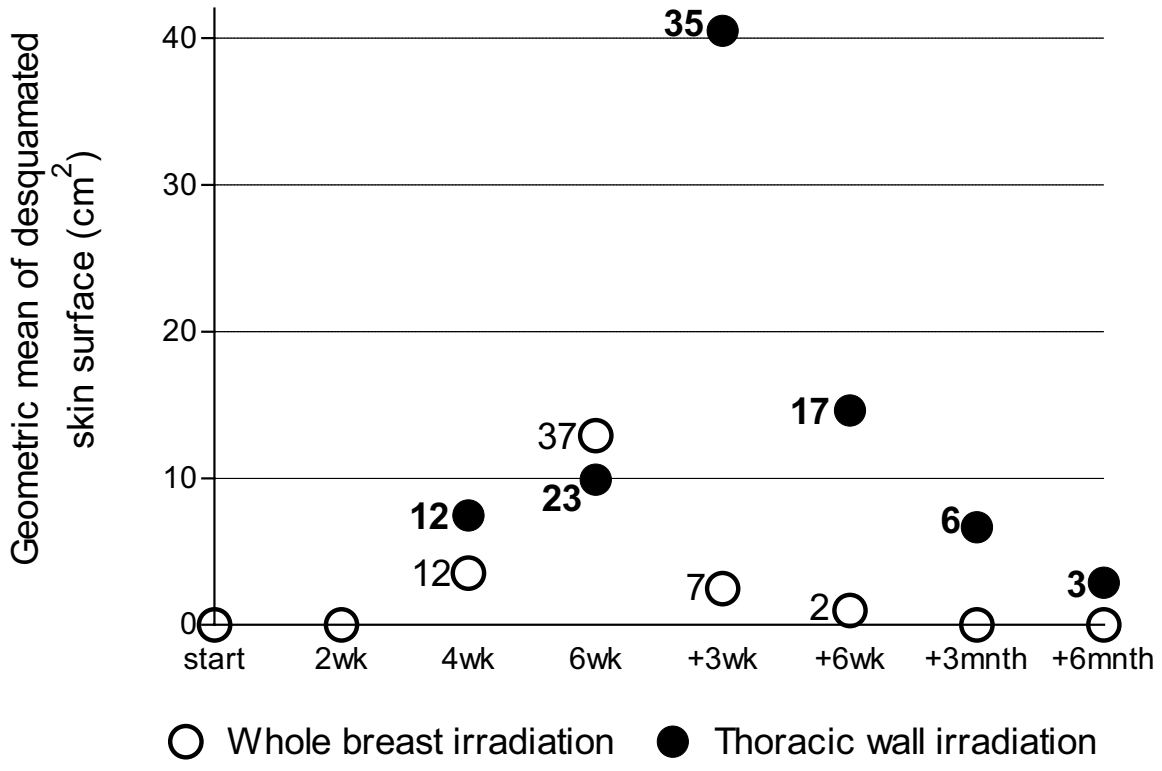
Age and type of primary surgical treatment were not significantly associated with the end-points and are therefore not shown.

n.s, not significant; O.R., odds ratio; 95% C.I., 95% confidence interval; CT, chemotherapy, RT, radiotherapy; AC, doxorubicin-cyclophosphamide; CMF, cyclophosphamide-methotrexate-fluorouracil; MRM, modified radical mastectomy; BCT, breast conserving therapy.

analysis was performed. The results are given in Table 8.4. The administration of CT/RT, compared with RT, was associated with significantly more high-grade skin toxicity, oesophagitis/dysphagia, dyspnoea, malaise, anorexia and nausea. After adjustment for the other potential risk factors, when the AC/RT group was compared with the CMF/RT group, a borderline significance was noted

specifically with respect to more high-grade skin toxicity (P=0.05, odds ratio (OR) 2.4). There was also a trend towards more high-grade oesophagitis/dysphagia, anorexia and nausea in patients receiving AC/RT compared with patients receiving CMF/RT (p=0.06-0.08, OR 2.1-2.6) (Table 8.4). The inclusion of regional lymph node areas in the radiotherapy regimen was associated with significantly more high-grade skin-toxicity and oesophagitis/dysphagia. The type of primary surgical treatment was not significantly associated with any of these endpoints.

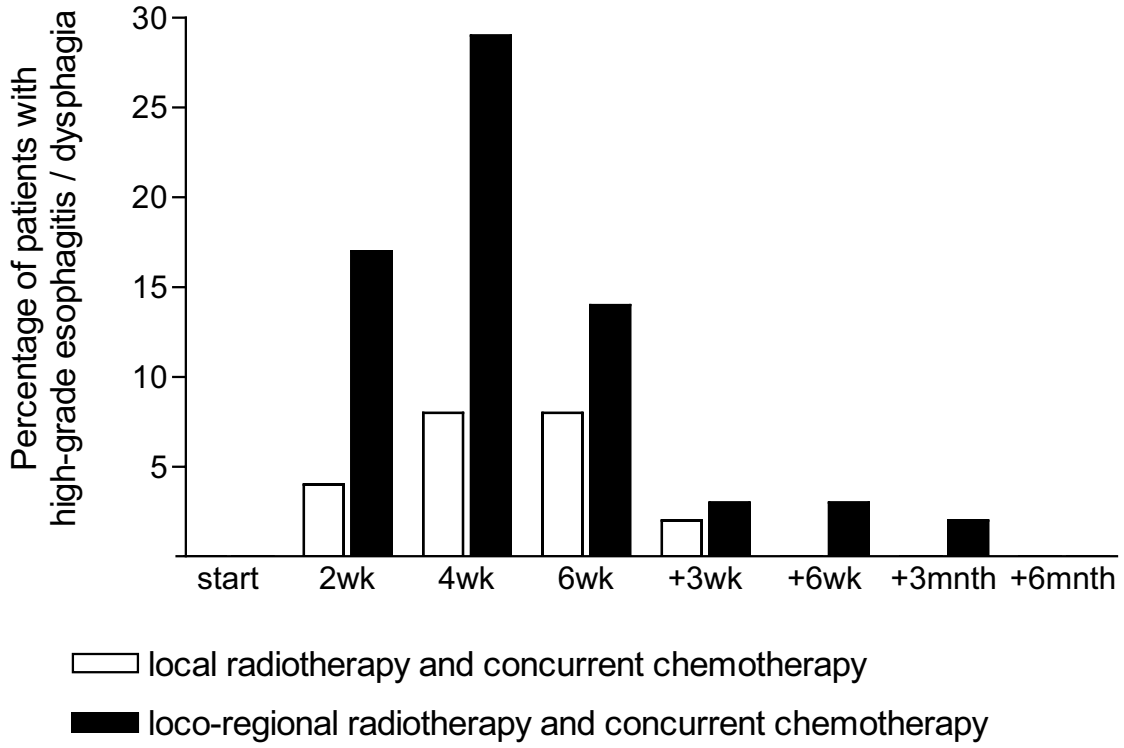
Figure 7.1. The effect of radiotherapy on the geometric mean of desquamated skin surface area in patients treated with concurrent radio- and adjuvant chemotherapy, 2 weeks, 4 weeks and 6 weeks after start of radiotherapy, and 3 weeks, 6 weeks, 3 months and 6 months after completion of radiotherapy. Geometric means of areas of desquamated surface are presented together with number of patients involved.



The administration of CT/RT was, after adjustment for the other potential risk factors, associated with significantly more hospital admissions. During the follow-up, 19 of 112 patients (17%) treated with CT/RT were (in total 30 times) admitted to hospital with acute complications of treatment. Only 1 patient (2%) treated with RT only was admitted to hospital. The median duration of hospital admissions was 11 days (range 2-64 days). More than half of the hospital admissions was related to local toxicity in the irradiated area. A dose reduction of chemotherapy to less than 85% of the planned dose was necessary in 12 patients (11%) and was independent of treatment regimen, tumour and patient characteristics.

The duration of high-grade skin toxicity was significantly longer after TWI (median 34 days) than after WBI (median 22 days) (p=0.02). The geometric mean value of surface areas of skin desquamation was higher after TWI than that after WBI (Figure 8.1). After WBI 41 patients (38%) developed high-grade skin toxicity for a median period of 22 days (range 14 – 92 days). After TWI 37 patients (79%) developed high-grade skin toxicity for a median of 34 days (range 14 –221 days). Six weeks after the completion of radiotherapy, 19 patients had not recovered from high-grade skin toxicity. All 19 patients had received concurrent chemotherapy and radiotherapy on the regional lymph nodes (including WBI or TWI). Six months after completion of radiotherapy 3 patients still had high-grade skin toxicity. The incidence of high-grade toxicity of the oesophagus was significantly higher in patients treated with loco-regional radiotherapy compared with that in patients treated with local radiotherapy (Figure 8.2), but the duration of complaints did not differ significantly. 33 patients developed high-grade oesophagitis/dysphagia for a median duration of 16 days (range 9 – 217 days). 109 patients developed high-grade malaise for a median duration of 64 days (range 13 – 224 days). The duration of high-grade skin toxicity, oesophagitis/dysphagia and malaise, and the maximum surface area of skin desquamation, was not associated with the type of chemotherapy.

Figure 7.2. The effect of concurrent chemotherapy and local and loco-regional radiotherapy on the prevalence of high-grade oesophagitis/dysphagia 2 weeks, 4 weeks and 6 weeks after start of radiotherapy, and 3 weeks, 6 weeks, 3 months and 6 months after completion of radiotherapy.



DISCUSSION

For breast cancer patients, the optimal sequence of radiotherapy and adjuvant chemotherapy is not clearly defined. Theoretically, one can expect the largest treatment benefit when both modalities are given concurrently.[7] However, it has been reported that the concurrent administration of the two modalities leads to an increased incidence of side effects.[8] In retrospective studies on the combination of chemotherapy and radiotherapy the following results were reported: a worsened cosmetic outcome after breast conserving therapy;[9,10] an increased

level of haematological toxicity;[11] an increased incidence of severe skin toxicity;[12,15] a higher incidence of radiation pneumonitis[11,14] and arm oedema.[13] Moreover it has been reported that an increased level of toxicity compromises an optimal dose delivery, with respect to both radiotherapy and chemotherapy.[15,18] In some retrospective studies, however, no or only a minor increase in toxicity has been found when chemotherapy and radiotherapy were given concurrently.[13,18,22]

The enhancement of side effects of radiation by chemotherapy does not only depend on the sequencing of radiotherapy and chemotherapy, but also on the type of cytotoxic drugs used. Skin effects are more frequently reported with the use of doxorubicin and 5-Fluorouracil.[17] Others found that doxorubicin in particular potentiated the effect of radiotherapy on the skin and the normal mucosa of the oesophagus.[16] In the present study, we prospectively compared the acute toxicity of two commonly used adjuvant chemotherapy regimens (CMF and AC) administered concurrently with radiotherapy. A third group treated with radiotherapy only was added.

Others have already stated that although conservative surgery combined with breast irradiation is associated with low incidences of significant (late) complications, both cosmetic result en the risk of complications can be unfavourably influenced by the addition of nodal irradiation and/or chemotherapy.[8] In the present study, the addition of adjuvant chemotherapy, concurrent with radiotherapy, did increase the risk of acute toxicity. CT/RT, AC/RT more than CMF/RT, caused a higher incidence of high-grade skin toxicity than RT alone. However, the inclusion of regional nodal areas in the irradiation field was of greater importance. As shown in Table 8.5, almost 90% of patients treated with concurrent AC and loco-regional radiotherapy developed high-grade skin toxicity compared with 44% of patients treated with concurrent AC and local radiotherapy. TWI was the main predictor of duration of high-grade skin toxicity and of the extent of desquamated skin surface. This could be explained by the fact that, in

cases of TWI, tissue equivalent material was applied on the skin to ensure a 100% skin dose. In contrast, during WBI (as part of radiotherapy during BCT), no tissue equivalent material was used, resulting in a lower skin dose of approximately 75%. In our multivariate analysis, TWI was not significantly related to the incidence of high-grade skin toxicity.

Loco-regional radiotherapy (encompassing the oesophagus) and the addition of concurrent chemotherapy to radiotherapy were the most important risk factors for developing high-grade oesophagitis/dysphagia. There was a trend towards more high-grade oesophagitis/dysphagia when AC/RT was administered instead of CMF/RT. As shown in Table 8.5, more than half of all patients treated with loco-regional radiotherapy concurrent with AC developed high-grade oesophagitis/dysphagia, compared with only 12% of patients treated with local radiotherapy (and hence no irradiation of the oesophagus) concurrent with AC.

In the present study, symptomatic radiation pneumonitis was observed in only a small proportion of patients. Grade 2 pneumonitis (requiring steroid treatment) was seen in 2% of patients treated with RT and in 4% of patients treated with CT/RT. Because of these low incidences of pneumonitis, it was not possible to draw any further conclusions. Lingos and colleagues retrospectively reviewed 1624 breast cancer patients for the risk of developing radiation pneumonitis.[14] They concluded, in line with our observations, that radiation pneumonitis following conservative surgery and radiation therapy for breast cancer is a rare complication, but that it was more likely to occur in patients treated with both loco-regional radiotherapy and chemotherapy (particularly when given concurrently with radiation therapy). Others found similar results.[13] In the present study, the administration of chemotherapy concurrently with radiotherapy did cause significant more dyspnoea on exertion. But only 5% of patients (in all three groups) experienced dyspnoea at normal levels of activity, and only one patient

experienced dyspnoea at rest. We found no difference in incidence of lung toxicity between CMF/RT and AC/RT.

Table 7.5. Acute toxicity, hospital admissions and chemotherapy dose reduction according to radiotherapy- and chemotherapy regimen.

	Local radiotherapy			Loco-regional Radiotherapy		
	RT	**CMF/RT**	**AC/RT**	**RT**	**CMF/RT**	**AC/RT**
High-grade skin toxicity	20%	25%	44%	42%	74%	89%
High-grade skin toxicity six weeks after completion of radiotherapy	0%	0%	0%	0%	30%	36%
High-grade oesophagitis/dysphagia	3%	7%	12%	8%	30%	53%
Hospital admissions	3%	11%	8%	0%	22%	25%
Chemotherapy dose reduction (< 85%)		7%	4%		17%	14%

RT, radiotherapy; AC, doxorubicin-cyclophosphamide; CMF, cyclophosphamide-methotrexate-fluorouracil

The administration of chemotherapy was the sole risk factor for developing high-grade malaise, anorexia, nausea, vomiting and fever. There was a trend towards more high-grade anorexia and nausea in the group of patients receiving AC/RT compared with the group of patients receiving CMF/RT. In the RT group high-grade malaise, anorexia, nausea, vomiting and fever hardly developed. In the chemotherapy groups, nausea, vomiting and fever were mainly limited to grade 2 (moderate) toxicity level.

As shown in table 8.5, the risk of acquiring a complication necessitating hospital admittance was higher during or after a concurrent chemotherapy and loco-regional radiotherapy regimen than after than after local RT. More than 20% of patients treated with concurrent loco-regional radiotherapy and chemotherapy compared with approximately 10% of patients treated with concurrent local radiotherapy and chemotherapy and 3% of patients treated with radiotherapy alone were admitted to hospital. In addition, more patients received an inadequate dose of chemotherapy when chemotherapy was combined with concurrent loco-regional radiotherapy. When chemotherapy was combined with local radiotherapy approximately 5% of patients received an inadequate dose, compared with approximately 15% of patients when chemotherapy was combined with loco-regional radiotherapy (Table 8.5). Denham and colleagues also found a trend towards a lower mean delivered fraction of planned dose of chemotherapy while extending the radiation field.[18] Dubey and colleagues studied the delivery of CMF concurrent with a reduced, local radiotherapy regimen. Seven percent of patients received inadequate drug doses.[15]

We conclude that in the treatment of patients with early breast cancer, the administration of adjuvant chemotherapy concurrently with loco-regional radiotherapy is too toxic. In particular, more skin desquamation and moderate to severe oesophagitis/dysphagia can be anticipated. In addition, more than 20% of patients need to be admitted to hospital with acute complications of therapy, and approximately 15% of patients receive less than 85% of the planned dose of chemotherapy. The concurrent administration of local radiotherapy to the breast and chemotherapy is less toxic. However, the administration of local radiotherapy concurrent with AC still leads to high-grade skin toxicity in 44% of patients. As anthracyclin-containing regimens, in particular 4 courses of AC, are considered standard for adjuvant chemotherapy in early breast cancer in many countries, the concurrent administration of adjuvant chemotherapy and radiotherapy is not recommended.

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