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CLINICAL INVESTIGATION **Breast**

HYPOFRACTIONATED AND ACCELERATED RADIOTHERAPY WITH SUBCUTANEOUS AMIFOSTINE CYTOPROTECTION AS SHORT ADJUVANT REGIMEN AFTER BREAST-CONSERVING SURGERY: INTERIM REPORT

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Purpose: Short radiotherapy schedules might be more convenient for patients and overloaded radiotherapy departments, provided late toxicity is not increased. We evaluated the efficacy and toxicity of a hypofractionated and highly accelerated radiotherapy regimen supported with cytoprotection provided by amifostine in breast cancer patients treated with breast-conserving surgery.

Methods and Materials: A total of 92 patients received 12 consecutive fractions of radiotherapy (3.5 Gy/fraction for 10 fractions) to the breast and/or axillary/supraclavicular area and 4 Gy/fraction for 2 fractions to the tumor bed). Amifostine at a dose of 1,000 mg/d was administered subcutaneously. The follow-up of patients was 30–60 months (median, 39).

Results: Using a dose individualization algorithm, 77.1% of patients received 1,000 mg and 16.3% received 750 mg of amifostine daily. Of the 92 patients, 13% interrupted amifostine because of fever/rash symptoms. Acute Grade 2 breast toxicity developed in 6.5% of patients receiving 1,000 mg of amifostine compared with 46.6% of the rest of the patients ($p < .0001$). The incidence of Grade 2 late sequelae was less frequent in the high amifostine dose group (3.2% vs. 6.6%; p = NS). Grade 1 lung fibrosis was infrequent (3.3%). The in-field relapse rate was 3.3%, and an additional 2.2% of patients developed a relapse in the nonirradiated supraclavicular area. c-erbB-2 overexpression was linked to local control failure ($p = .01$). Distant metastasis appeared in 13% of patients, and this was marginally related to more advanced T/N stage ($p = .06$).

Conclusion: Within a minimal follow-up of 2.5 years after therapy, hypofractionated and accelerated radiotherapy with subcutaneous amifostine cytoprotection has proved a well-tolerated and effective regimen. Longer follow-up is required to assess the long-term late sequelae. © **2009 Elsevier Inc.**

Hypofractionation, Acceleration, Radiotherapy, Amifostine, Breast cancer, c-erbB-2 expression.

INTRODUCTION

Postoperative radiotherapy (RT) after breast-conserving surgery is the standard of care for patients with early-stage breast cancer (1). The largest experience of breast RT has been with standard fractionation, which demands long treatment schedules of 6–7 weeks. The establishment of safe and effective short RT regimens would help to simplify adjuvant RT for early breast cancer. Novel approaches of partial breast RT using interstitial implants or conformal RT techniques are under investigation for patients with small tumors (2, 3). Such techniques deliver the desired dose within a short treatment time, but their efficacy in terms of local control remains as yet unknown.

Whole breast RT with larger daily doses (hypofractionation) condenses the RT regimen to 6–16 fractions, drastically reducing the workload of RT departments and the discomfort of patients who reside at long distances from RT centers. The Canadian study showed that the administration of a regimen shorter by 10 days offered equal efficacy to that of standard fractionation (4). The most recent randomized study, by Bentzen *et al.* (5), also showed that a 13-day regimen was equally effective to, and did not result in late toxicity worse than that of, standard fractionation. The main criticism against hypofractionation is the very-long-term, >10 years, unknown rates of lung or cardiac toxicity (6). The incidence of second malignancies is also an issue that requires 20 years of follow-up (7), which has not yet been reached by any of the published clinical trials.

Whether cytoprotective agents, such as amifostine, could help to reduce radiation toxicities in breast cancer patients is obscure. A previous pilot study showed that hypofractionated accelerated RT with cytoprotection using intravenously

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Table 1. Patient, disease, and medical treatment characteristics

Characteristic	Value
Patients (*n*)	92
Age (y)	
Median	56
Range	26-78
Performance status 0 (*n*)	92
T stage (*n*)	
Tis	1
T1	51
T1, multifocal	3
T2	33
T3	4
N stage (*n*)	
N0	39
N1-N3	26
>N3	10
Extracapsular invasion	9
Unknown	8
Histologic features (*n*)	
NOS	84
Lobular	5
Myeloid	3
Grade (NOS) (*n*)	
1	15
2	29
3	40
ER status (*n*)	
Negative	27
Positive	65
HER-2 status (*n*)	
Negative	42
Positive	28
Unknown	22
Surgery (*n*)	
Conservative	92
Axillary dissection	84
Pre-RT chemotherapy (*n*)	
None	26
CMF	14
FEC	20
Taxane based	32
Hormonal therapy during RT (*n*)	
None	26
Tamoxifen	33
Amromatase inhibitors	33
LH-RH agonists	8
Tastuzumab during RT (*n*)	
No	76
Yes	16

Abbreviations: NOS = not otherwise specified; ER = estrogen receptor; RT = radiotherapy; CMF = cyclophosphamide, methotrexate, and 5-fluorouracil; FEC = 5-fluorouracil, epirubicin, and cisplatin; LH-RH = luteinizing hormone-releasing hormone.

administered amifostine (HypoARC) provided encouraging results, with minimal early and late toxicity and improved efficacy in specific subgroups of patients (8, 9). Since 2003, a prospective study has been on-going, recruiting patients with early-stage breast cancer to receive HypoARC to the breast and/or axilla and supported with high-dose, daily, subcutaneously administered, amifostine. An interim analysis focusing on the early and short-term late toxicities is presented. The efficacy of the regimen in terms of local control and survival is also reported. Moreover, this study focused on the role of the histologic and molecular features on local tumor control and metastasis.

METHODS AND MATERIALS

Between January 2003 and September 2005, at the Department of Radiotherapy and Oncology, University Hospital of Alexandroupolis, Greece, 92 breast cancer patients, who had undergone breast-conserving surgery with ($n = 84$) or without ($n = 8$) axillary lymph node dissection, were recruited to the present study to assess the toxicity and efficacy of HypoARC as an adjuvant regimen. A minimal follow-up of 30 months was allowed before analysis of the data. The median follow-up for the patients alive was 39 months (range, 30–60). Before the analysis, all patients underwent clinical examination, recent computed tomography (CT) scans were reviewed by two observers, and any toxicity was recorded by consensus.

Patient recruitment

All patients had a performance status of 0 (World Health Organization scale). Table 1 lists the patient, disease, and medical treatment characteristics. All patients provided written informed consent. It was clearly explained to the patients that hypofractionation is still considered an investigational approach for adjuvant breast cancer treatment. The local ethics and scientific committees approved the study. Most patients participating in the study reported that the shorter duration of the treatment schedule was their major reason for joining the protocol.

Evaluation before and during treatment

The baseline studies included physical examination, blood count measurement, complete biochemical profile, serum tumor marker (carcinoembryonic antigen, cancer antigen 15-3, cancer antigen 19-9, and cancer antigen 125) determination, and chest/upper abdomen CT. Acute radiation toxicity was monitored daily during therapy. Radiation toxicity was monitored once a week for 1 month after RT completion, every 3 months for the first year, every 4 months for the second and third years, and every 6 months thereafter. Disease status was also monitored with CT (chest/abdomen) and tumor serum marker measurement at the same follow-up visits. Mammography and/or breast ultrasonography was performed yearly.

The National Cancer Institute Common Toxicity Criteria, version 2, was used to assess the chemotherapy and acute radiation toxicity (available from: www.accessdata.fda.gov/scripts/cder/onctools/toxcrit2.cfm). The late effects of normal tissue–subjective, objective, management and analytic criteria were used for the clinical assessment of late sequelae (10). At some points, modifications were performed to simplify the grouping of toxicities, as determined by us (Tables 2 and 3).

RT technique

Radiotherapy was delivered using a 6/18-MV linear accelerator (Electa, Stockholm, Sweden) with a multileaf collimator after CT simulation and conformal RT planning (Plato, Nucletron, Veenedaal, The Netherlands). RT was given to the breast using tangential fields. The dose distribution was optimized using appropriate wedges and mixed 6/18-MV energy fields when necessary. The dose distribution was calculated at the maximal dose point. The isodose curve for the calculation of the dose was chosen to allow less than a $\pm 3\%$ variation of the dose in the breast and no more than

Table 2. Early toxicity assessed with National Cancer Institute Common Toxicity Criteria version 2 (n = 92)

Toxicity	Patients (n)
Radiation dermatitis	
0. None	27 (29.4)
1. Faint erythema/dry desquamation	47 (51.0)
2. Brisk erythema/patchy moist desquamation	18 (19.6)
3. Confluent moist desquamation	0 (0)
4. Skin necrosis	0 (0)
Breast desquamation	
0. None	45 (48.9)
1. Dry desquamation	31 (33.6)
2. Patchy moist desquamation	16 (17.4)
3. Confluent moist desquamation	0 (0)
Breast erythema	
0. None	52 (56.5)
1. Faint erythema	29 (31.5)
2. Brisk erythema	11 (12.0)
Breast edema (as modified in present study)	
None	67 (72.8)
Barely palpable/asymptomatic	23 (25.0)
Moderate/tolerable	2 (2.2)
Severe/requiring therapy	0 (0)
Pain (breast/chest wall/arm)	
None	81 (88.0)
Mild	9 (9.8)
Moderate	2 (2.2)
Severe	0 (0)
Pneumonitis	
None	92 (100)
Radiographic changes/asymptomatic	0 (0)
Radiographic changes/symptomatic/steroids	0 (0)
Radiographic changes/symptomatic/oxygen	0 (0)
Assisted ventilation required	0 (0)

Data in parentheses are percentages.

Table 3. Late toxicity assessed with LENT-SOMA/NCI simplified grading system (n = 92)

Toxicity	Patients (n)
Breast edema (as modified in present study)	
None	69 (75.0)
Barely palpable/asymptomatic	19 (20.6)
Moderate/tolerable	4 (4.4)
Severe/requiring therapy	0 (0)
Breast fibrosis	
None	78 (84.8)
Barely palpable	13 (14.1)
Definite firmness	1 (1.1)
Very marked firmness/fixation	0 (0)
Tumor bed breast fibrosis	
None	49 (53.3)
Barely palpable	37 (40.2)
Definite increased density	6 (6.5)
Firmness/fixation	0 (0)
Skin telangiectasia (as modified in present study)	
None	63 (68.5)
Sporadic in tumor bed	25 (27.1)
Intense in tumor bed	4 (4.5)
Outside tumor bed	0 (0)
Skin atrophy/ulceration (as modified in present study)	
None	92 (100)
Detectable	0 (0)
Marked	0 (0)
Chronic ulcer	0 (0)
Circumferential arm lymphedema	
None	88 (95.6)
2–4 cm	4 (4.4)
4–6 cm	0 (0)
>6 cm	0 (0)
Useless arm	0 (0)
Pain (breast/chest wall/arm)	
None	80 (87.0)
Mild	11 (11.9)
Moderate	1 (1.1)
Severe	0 (0)
Lung fibrosis (NCI scale)	
None	89 (96.7)
Radiographic changes/asymptomatic	3 (3.3)
Radiographic changes/symptomatic/steroids	0 (0)
Radiographic changes/symptomatic/oxygen	0 (0)
Assisted ventilation required	0 (0)

Abbreviations: LENT-SOMA = late effects of normal tissue–subjective, objective, management and analytic criteria; NCI = National Cancer Institute.

Data in parentheses are percentages.

a +10% greater dose in small hot spots (usually located at the outer and inner edge of the tangential fields). The angle of the tangential fields and the inner and outer limits were carefully designed to allow the least possible dose distribution to the lungs. The inner mammary lymph nodes were not irradiated.

The upper axillary and supraclavicular areas were also irradiated through a direct 18-MV field in patients with more than three involved nodes and/or with extracapsular node invasion or in patients who had not undergone axillary dissection. The calculation of the dose distribution was performed at the maximal dose point and the 85% ± 2% isodose curve was used for the dose calculation. A wedge of 10°–15° (directed to the body midline) was usually applied to allow for a deeper isodose distribution in the axilla than in the supraclavicular area.

The same fractionation was used for breast and supraclavicular RT. Patients received a daily fraction of 3.5 Gy to a total dose of 35 Gy (10 consecutive fractions) within 12 days. An additional dose of 8 Gy (4 Gy/fraction) was given to the tumor-residing breast quadrant using electrons (8–12 MeV). A posterior axillary field delivered an additional fraction of 3.5 Gy to the axilla. The overall treatment time was 16 days.

The normalized total dose (NTD) was calculated using the formula proposed by Macejewski *et al.* (11): $NTD = D\ [(\alpha/\beta + d)/(\alpha/\beta + 2)]$, where D is the total physical dose, d is the dose per fraction, and α/β is the tissue-specific ratio. The NTD corrected for the overall treatment time was calculated using a previously proposed formula (8): $NTD_{(T)} = D\ [(\alpha/\beta + d)/(\alpha/\beta + 2)] + \lambda(Tc - To)$, where Tc is the number of days required for the delivery of the NTD using a conventionally fractionated scheme, To is the number of days required for the delivery of the current scheme, and λ is the estimated daily dose consumed to compensate for rapid tumor repopulation. For cancer and normal breast area tissues, an α/β ratio of 4 Gy was considered, as calculated by Bentzen *et al.* (5). For cancer cells, a λ-value of 0.4 Gy was considered. For normal tissues, a λ-value of 0.2 Gy was adopted in the radiobiologic calculations. The specific biologic dosimetric analysis of the regimen is presented in Table 4.

Amifostine administration

Tropisetron 10 mg was administered orally, 30–60 min before amifostine injection as an antiemetic. Amifostine 1,000 mg was

Table 4. Radiotherapy schedule, physical dose, normalized total dose, and normalized total dose with time correction delivered to normal and cancer tissues

Tissue	Dose (Gy/fraction) × (fractions *[n]*)	Physical dose (Gy)	NTD(n,c) (Gy)	Treatment (d)	Accelerated* (d)	NTD-T(n) (Gy)	NTD-T(c) (Gy)
Breast	3.5 × 10	35	43.75	12	18	47.35	50.90
Tumor bed	+ 4 × 2	43	54.40	16	21	58.60	62.80
Axilla†	3.5 × 11	38.5	48.10	15	20	52.10	56.10

Abbreviations: NTD(n,c) = normalized total dose to normal and cancer tissue, respectively, calculated for α/β = 4 Gy; NTD-T(n) = NTD corrected for time delivered to normal tissues calculated for λ = 0.2 Gy; NTD-T(c) = NTD corrected for time delivered to cancer calculated for λ = 0.4 Gy.

* Days of acceleration of radiotherapy

† Patients with >3 positive nodes or with extracapsular invasion or who did not undergo axillary dissection.

diluted in 5 mL of water for injection and was injected at two sites (usually the right and left shoulders), with the patient sitting. A blood pressure assessment was not performed, because this is not necessary when amifostine is given subcutaneously (12). The greater dose of amifostine (1,000 mg instead of 350–500 mg used in other studies) applied in the protocol was chosen to better protect the tissues against the large RT fractions in the HypoARC scheme.

The total dose of 1,000 mg was reached gradually (Day 1, 500 mg; Day 2, 750 mg; and Day 3, 1,000 mg) using a previously published algorithm (12). The tolerance of patients to amifostine was recorded daily using a scoring system (12). The tolerance of the patients to amifostine was scored as good/acceptable, poor, or unacceptable for each dose level. If at any point, the patients experienced unacceptable nausea/emesis or fatigue, dexamethasone 8 mg was administered intramuscularly before amifostine and the tolerance was reassessed the next day. If good tolerance was confirmed, amifostine administration was continued as prescribed. If not, the dose was reduced to 750 mg and, if necessary, to 500 mg. If the patients did not tolerate the dose of 500 mg well, the use of amifostine was interrupted. No more than two dexamethasone injections were allowed per week of RT. Fever/rash attributed to amifostine (or to any other drug) resulted in the permanent interruption of amifostine and oral administration of corticosteroids and antihistamines for 2–3 days (12).

Immunohistochemistry

An immunohistochemical streptavidin-biotin technique was used for the detection of c-erbB-2 and estrogen receptor (ER) expression, as previously described (9). The percentage of tumor cells with membrane c-erbB-2 staining was recorded in all optical fields, and a mean value of ≥20% was considered positive. Positive tumors were classified into two groups: tumors with high c-erbB-2 reactivity (20–50% positive cells) and those with very high c-erbB-2 reactivity (50–100% positive cells). For ER expression, those with nuclear reactivity in ≥20% of cells were considered positive.

Statistical analysis

The statistical analysis and graph presentation of the survival curves was performed using the GraphPad Prism, version 5.00, and the GraphPad Instat (San Diego, CA) packages. Fisher's exact test or the unpaired two-tailed *t* test was used to compare categorical variables, as appropriate. Survival curves were plotted using the Kaplan-Meier method, and the log–rank test was used to determine statistically significant differences between life tables. The patient- and treatment-related variables were also analyzed in multivariate stepwise logistic regression models. Values with $p < .05$ were considered statistically significant.

RESULTS

Amifostine tolerance

Using the dose individualization algorithm, 71 (77.1%) of the 92 patients received 1,000 mg of amifostine, 15 (16.3%) received 750 mg, and 2 (2.2%) received 500 mg. Another 4 patients (4.4%) did not tolerate the dose of 500 mg (unacceptable fatigue and/or vomiting), and amifostine was discontinued. Fever and/or rash appeared in 12 (13.6%) of 88 patients (3 of 17 and 9 of 71 receiving 500–750 mg and 1,000 mg, respectively; $p = .69$). Fever and/or rash appeared within a median of 7 days (range, 3–9) of therapy. No case of necrolytic syndrome, clinical hypotension, or hypoglycemia was noted. At the individualized dose established, the patients had an excellent tolerance with mild and tolerable nausea and fatigue in 15 of 88 cases.

Acute radiation toxicity

During the 16 days of therapy, the patients did not report any discomfort apart from the occasional feeling of heaviness in the breast. Table 2 lists the findings of the clinical examination performed 7 days after RT completion. The peak of toxicity, when it appeared, occurred 5–10 days after RT completion and had regressed completely within 1–2 weeks.

Of the 92 patients, 27 (19.4%) had no skin toxicity at all, 47 (51%) had Grade 1 toxicity, and 18 (19%) presented with spots of Grade 2 dermatitis. At 14 days after RT, a net regression of dermatitis was obvious, with no case of persistent moist desquamation. At 1 month after RT, a faint/mild increase in the skin pigmentation was a common finding.

Barely palpable, asymptomatic breast edema was noted in 25% of patients, and evident edema was noted in 2.2%. Mild breast pain was reported by 9.8% and moderate pain by 2.2% of patients. Analgesics were not used by any of the patients. No case of acute pneumonitis or radiation plexopathy was recorded.

Overall, Grade 2 breast acute toxicity was noted in 18 (19.6%) of 92 patients, grade 1 in 53 (57.6%), and grade 0 in 21 (22.8%). An analysis according to the total dose of amifostine received (taking also into account interruptions due to fever/rash) showed that a daily dose of amifostine of 1,000 mg offered significantly better cytoprotection. Grade

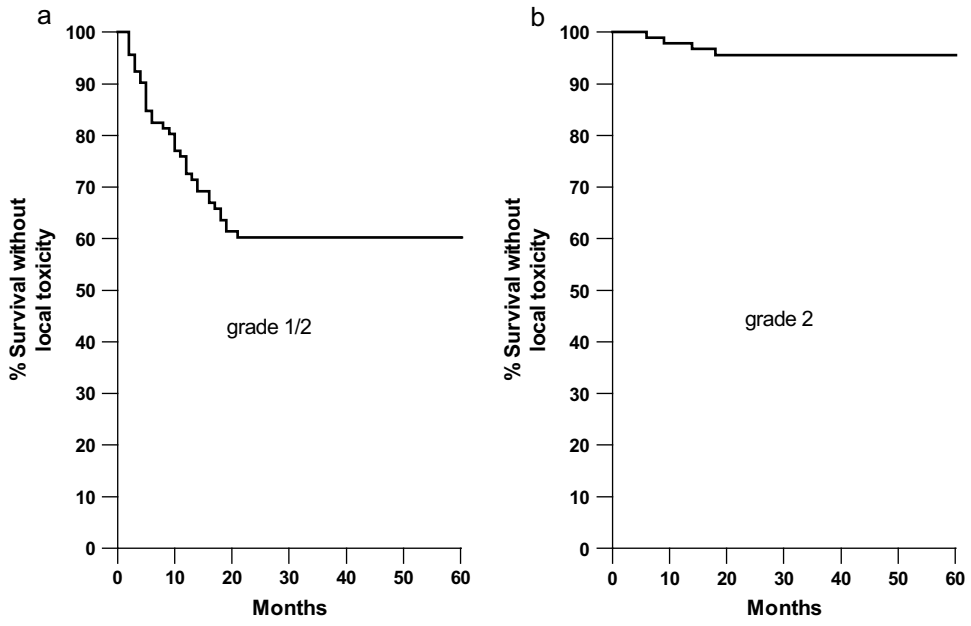

Fig. 1. Late effect-free Kaplan-Meier survival curves.

2 acute toxicity was noted in 4 (6.5%) of 62 patients who received a daily dose of the full 1,000 mg of amifostine compared with 14 (46.6%) of 30 patients receiving a lower amifostine dose ($p < .00001$).

Late radiation toxicity

Table 3 lists the short-term late toxicity recorded within a median follow-up of 39 months (range, 30–60). Overall, the lack of breast edema and/or fibrosis was confirmed in 65 (70.6%) of 92 patients, and Grade 1 toxicity was noted in 23 patients (25%). Grade 2 breast edema and/or fibrosis was noted in 4 (4.4%) of 92 patients. In the tumor bed, however, palpable fibrosis was more frequent (37 of 92, 40.2%), and it was intense in 6 (6.5%) of the 92 patients. Within the tumor bed, dense telangiectasia appeared in 4.5% of patients. Mild breast soreness was reported by 11.9% of patients, and 1 patient (1.1%) complained for persistent breast pain that did not require analgesics. No case of skin atrophy, ulceration, or fat necrosis was noted.

Grade 1 arm edema appeared in 4.4% of patients, but no patient developed axillary fibrosis or brachial plexopathy. None of the patients developed a rib fracture or thoracic muscle fibrosis. On CT performed during the follow-up period, increased lung density within the tangential fields and/or the irradiated pulmonary apex was recorded in 3 (3.3%) of the 92 patients. No case of symptomatic lung fibrosis was noted.

Overall, Grade 2 late toxicity was noted in 4 (4.4%), grade 1 in 32 (34.8%), and grade 0 in 56 (60.8%) of 92 patients. The incidence of Grade 2 late sequelae was 3.2% in patients treated at the full 1,000 mg/d schedule compared with 6.6% in patients treated at lower doses (p = NS).

All Grade 2 and most Grade 1 late toxicities noted had occurred within 6–18 months from RT, and no deterioration was recorded thereafter. Figure 1a,b shows the Kaplan-Meier late effect-free survival curves for combined Grade 1-2 and Grade 2 toxicities. The estimated Grade 1-2 toxicity rate was 39.75% at 21 months, with no increase was predicted thereafter. The estimated incidence of Grade 2 toxicity at 18 months was 4.5%, with no additional increase with time.

In the multivariate analysis models, patient age, pretreatment hemoglobin level, previous chemotherapy, administration of trastuzumab, and amifostine dose level were not linked to the development of Grade 1-2 (or Grade 2) late toxicity (Table 5).

Survival analysis

At the present analysis, 3 (3.3%) of the 92 patients had developed a relapse within the radiation fields (two in the breast and one in the axilla). An additional 2 patients who had been node negative (2.2%) developed a relapse outside the radiation portals at the supraclavicular area. No relapse occurred in the nonirradiated internal mammary node area. The locoregional relapse-free survival curve is shown in Fig. 2a. The T/N stage and ER positivity were not related to locoregional

Table 5. Multivariate analysis of effect of variables on late toxicity (grade 1-2 and grade 2)

	Grade 1 and 2		Grade 2	
Variable	*t* Ratio	*p*	*t* Ratio	*P*
Age	0.79	.43	0.94	.34
T stage	0.34	.73	0.28	.77
N stage	0.20	.83	1.28	.20
Pre-RT chemotherapy	0.85	.39	0.88	.37
Trastuzumab	1.25	.21	0.45	.64
Hemoglobin level	1.54	.12	0.24	.81
Amifostine dose level	0.27	.78	1.00	.32

Abbreviation: RT = radiotherapy.

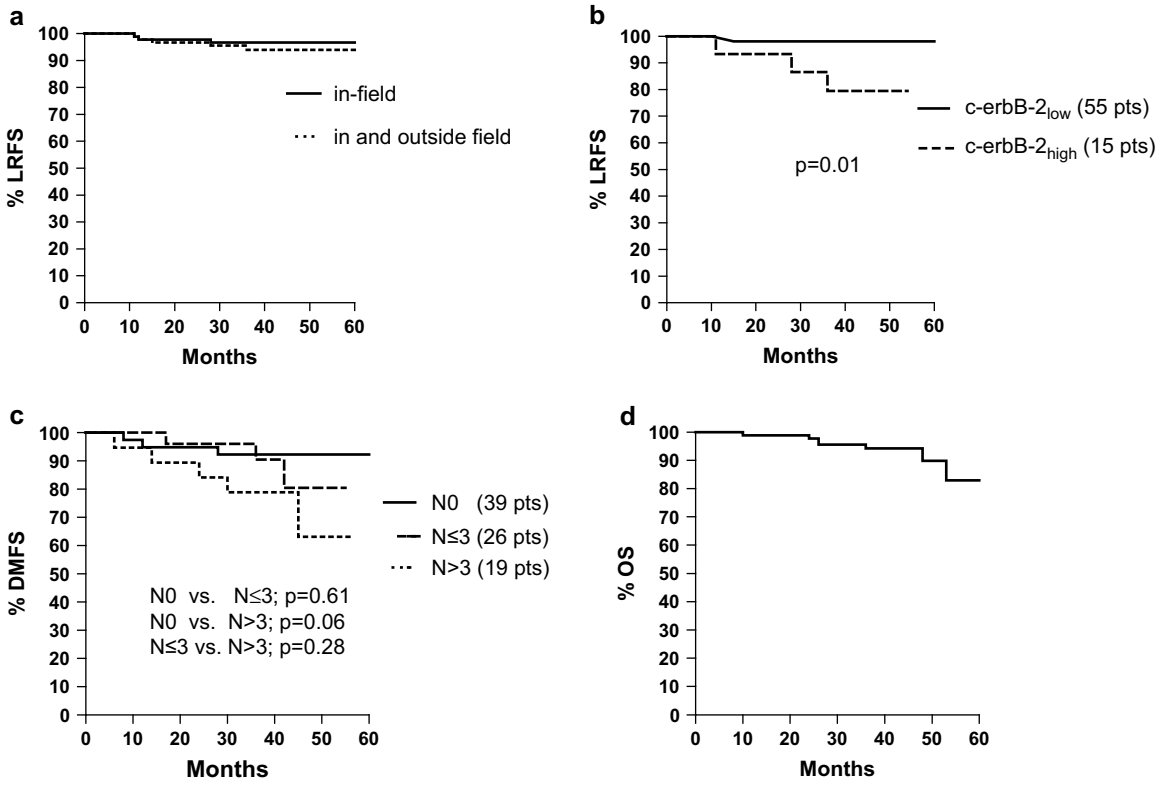

Fig. 2. Kaplan-Meier survival curves. (a) Local relapse-free survival (LRFS). (b) Local relapse-free survival (LRFS) stratified by c-erbB-2 expression. (c) Distant metastasis-free survival (DMFS) stratified by lymph node involvement. (d) Overall disease-specific survival (OS).

relapse-free survival curve. Very intense c-erbB-2 expression (>50% positive cells) was significantly associated with a poor locoregional relapse-free survival curve (Fig. 2b; $p = .01$). No association was found between previous exposure to adjuvant chemotherapy and local control. On multivariate analysis, c-erbB-2 expression was the only variable showing a marginal association with local relapse ($p = .08$, t ratio = 1.80; Table 6).

Overall, 12 (13%) of the 92 patients presented with distant metastasis, including all 5 patients with local relapse. Those with Stage T1 and Stage N0-N1 (Fig. 2c) had a marginally lower incidence of metastasis compared with those with more advanced stages ($p = .06$ and $p = .06$, respectively). c-erbB-2 overexpression (>20% positive cancer cells) showed a trend toward a high incidence of metastasis ($p = .09$). No association between distant metastasis and ER expression was noted.

The overall (disease-specific) survival of patients is shown in Fig. 2d. Seven patients had died at this analysis. The 60-month projected overall survival rate was 83%. T stage was not related to overall survival. Patients with more than three positive nodes and/or extracapsular invasion had a marginally poorer prognosis ($p = .06$). No significant association between overall survival and c-erbB-2 or ER expression was noted. Patients who had received adjuvant chemotherapy based on taxanes and/or anthracyclines had a worse prognosis ($p = 0.05$) than those who had not received chemotherapy, presumably a result of the more advanced stage of patients demanding adjuvant chemotherapy. None of the parameters examined had an independent prognostic value in the multivariate models (Table 6). However, the N stage approached significance ($p = .06$, t ratio = 1.90).

DISCUSSION

Radiotherapy after surgery confers an important benefit in the local control and overall survival of patients, whether applied after mastectomy or after breast-conserving surgery (1, 13). Chemotherapy also has a definite effect at the

Table 6. Multivariate analysis of effect variables on local relapse and death events

	Local relapse		Death events	
Variable	t Ratio	p	t Ratio	p
Age	0.12	.90	0.32	.74
T stage	1.05	.30	0.26	.79
N stage	0.89	.37	1.90	.06
Grade	0.12	.89	1.29	.20
ER	0.72	.47	0.91	.36
PgR	0.31	.75	0.80	.42
c-erbB-2	1.74	.08	0.89	.37
Pre-RT chemotherapy	0.30	.76	0.24	.81
Hemoglobin level	0.55	.58	0.20	.83

Abbreviations: PgR = progesterone receptor; other abbreviations as in Table 1.

locoregional level (14, 15). In the Early Breast Cancer Trialists' Collaborative Group overview, chemotherapy reduced the hazard ratio for local recurrence to 0.63 and 0.70 for patients <50 years and 51–69 years, respectively (16). However, chemotherapy is not a substitute for RT in terms of local disease control (17). Large studies have suggested an important survival benefit from RT after breast-conserving surgery. In the Early Breast Cancer Trialists' Collaborative Group study (16), RT reduced the 15-year breast cancer mortality rate from 31.2% to 26.1% in node-negative patients and from 55.0% to 47.9% in node-positive ones. A study by Athas *et al*. (18) showed that a large percentage of breast cancer patients do not receive RT after breast-conserving surgery. This percentage has ranged from 30% to 50% in patients residing >75 miles from an RT center or women >70 years. This has undoubtedly disastrous effects on the efficacy of the cancer healthcare systems and increases the overall cost of cancer management.

The prolonged standard RT schedule that demands daily travel to the RT center for 30–35 working days is certainly a major reason of such failure to apply optimal therapy for breast cancer patients. Shorter regimens might render RT more appealing to patients, as was observed in our study. Additionally, given the high numbers of breast cancer patients treated with breast-conserving surgery, such schedules would greatly relieve the congestion of busy RT departments. Whether accelerated partial breast RT (conformal, intraoperative, or interstitial) will prove to have efficacy equal that of whole breast RT for early-stage disease is under intense investigation in ongoing randomized trials (2, 3). Quite mature studies from Canada and the United Kingdom on whole breast RT have provided encouraging evidence that short hypofractionated schedules might be as equally effective and tolerable as standard RT (4, 5).

Whether cytoprotection with amifostine will contribute to the decrease of early and late RT sequelae of such hypofractionated and accelerated regimens remains obscure. Given the carcinogenesis inhibition effect of amifostine (19), it would also be of interest to investigate an eventual benefit in terms of a reduced incidence of second malignancies, estimated for lung cancer at 3.7% (compared with 0.3% in the normal population) within 20 years after breast RT (7). The overall experience on the use of amifostine in breast cancer patients is limited. In a pilot prospective study, amifostine was safely administered intravenously to breast cancer patients undergoing a regimen similar to that of the present RT scheme (HypoARC) after conservative surgery or mastectomy (8). Presumably owing to the accelerated delivery of RT that eliminates the ominous effect of rapid tumor repopulation, HypoARC was more effective in tumors with a high proliferation index and c-erbB-2 expression (9). Early toxicity was significantly reduced, and short-term late toxicity was low.

Taking into account this initial positive experience, we began a prospective study of HypoARC in patients treated with breast-conserving surgery. Amifostine was given subcutaneously, a route of administration with several advantages as shown previously (20). A dose individualization algorithm allowed the optimization of the dose of amifostine according to the individual's tolerance of the drug (12). Thus, 77% of patients received 1,000 mg daily and 16% received 750 mg daily with excellent tolerance. Fever and/or rash appeared in 13% of patients, within the range expected from lower doses, and no case of necrolytic skin syndrome occurred. The choice to pursue a greater daily dose of amifostine was determined from experimental studies on dose-dependent cytoprotection (21). The only dose-defining clinical trial ever performed for amifostine (12) during RT suggested an excellent tolerance for doses greater than the 350–500-mg dose used arbitrarily in previous studies.

Acute radiation toxicity appeared within 1 week after RT completion. Patchy moist skin desquamation and/or brisk erythema appeared in 17.4% of patients, and this was the worse acute toxicity noted. This toxicity had rapidly regressed within 1–2 weeks. In a recent randomized study reporting the benefits of intensity-modulated RT compared with conventional RT using standard fractionation, the incidence of moist skin desquamation was 27.1% and 36.7% in the intensity-modulated RT and control groups, respectively, and the duration of symptoms seem to extend ≤4 weeks from the end of RT (22). The far less frequent and rapidly regressing skin toxicity noted in the present study is suggestive of an important skin cytoprotection conferred by amifostine. Significantly lower toxicity was noted in patients who received the full 1,000-mg/d schedule, with an incidence of Grade 2 acute toxicity as low as 6.5%.

The analysis for short-term late events was allowed after completion of ≥2.5 years of follow-up. Although late effects can occur many years after RT, 3 years has been the period within which most severe late RT sequelae appear (4, 5, 23, 24). From the European Organization for Research and Treatment of Cancer trial, one can determine from the value provided for patients receiving a boost to the tumor bed that two-thirds of cases of moderate and severe fibrosis had already appeared within 3 years after RT (20% incidence) (23). The incidence had increased to 28% at 6 years and 31% at 12 years after therapy (23). In our study, all Grade 2 late sequelae had appeared within 6–18 months of follow-up, and no new case or deterioration of the established cases occurred thereafter. The Kaplan-Meyer estimates from our data also showed a decreased incidence of new toxicities after the second year. The addition of a RT boost to the breast quadrant of the tumor increased the incidence of Grade 2 fibrosis to 6.5%, which was acceptable given the improvement in local control rates conferred by this practice (23). No case of brachial plexopathy and none of any type of severe Grade 3-4 complications has yet occurred. Asymptomatic, radiographically detectable, increased lung density within the radiation portals was noted in 3.3% of our patients. Overall, the incidence of Grade 2 late sequelae was less frequent when the daily amifostine dose received was 1,000 mg (3.3% vs. 6.6%), but the difference did not reach statistical significance. It should be stressed, however, that these encouraging results refer only to short-term late events and that longer follow-up >20 years is required to confirm the safety of the regimen.

The efficacy of the regimen was encouraging. The relapse rate within the radiation field was 3.3%, with an additional 2.2% of patients developing relapse to the nonirradiated supraclavicular area. A significant association between strong c-erbB-2 overexpression with local relapse within and outside the radiation portals was noted. In a recent study, c-erbB-2 overexpression, in the absence of steroid receptor expression, was linked to a shorter local relapse-free interval after postmastectomy RT (25). It is unknown whether concurrent administration of trastuzumab or even chemotherapy (anti-c-erbB-2 monoclonal antibody) would have averted the increased incidence of local relapse in this subgroup of patients (26).

CONCLUSION

The results of our study have shown that HypoARC with high-dose, subcutaneously administered amifostine is a well-tolerated regimen. The RT schedule, which was reduced by 4 weeks, is convenient for patients residing away from the RT center and reduces the workload of the RT department. The low incidence of short-term late effects we recorded and the sharply decreased incidence of severe Grade 2 toxicities after the second year of follow-up have been encouraging; however, we remain cautious regarding the long-term late effects.

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