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ORIGINAL ARTICLE

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Combined-modality treatment of inflammatory breast carcinoma: twenty years of experience at M. D. Anderson Cancer Center

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Abstract *Purpose*: To review the 20 years of experience at M. D. Anderson Cancer Center with a combined-modality approach against inflammatory breast carcinoma. *Patients and methods*: A total of 178 patients with inflammatory breast carcinoma were treated in the past 20 years at M. D. Anderson Cancer Center by a combined-modality approach under four different protocols. Each protocol included induction chemotherapy, then local therapy (radiotherapy or mastectomy), then adjuvant chemotherapy, and, if mastectomy was performed, adjuvant radiotherapy. Chemotherapy consisted of 5-fluorouracil, doxorubicin, and cyclophosphamide (FAC) with or without vincristine and prednisone (VP). In protocol D, patients received an alternate adjuvant chemotherapy regimen, methotrexate and vinblastine (MV), if they did not have a complete response (CR) to induction chemotherapy. *Results*: The median follow-up of live patients in group A was 215 months, in group B 186 months, in group C 116 months, and in group D 45 months. An estimated 28% of patients were currently free of disease beyond 15 years. At the time of analysis, 50 patients were alive without any evidence of disease. A further 12 patients died of intercurrent illness, and 15 patients were followed beyond 10 years without recurrence of disease. Among initial recurrence, 20% of patients had local failure, 39% systemic failure, and 9% CNS recurrence. Initial response to induction chemotherapy was an important prognostic factor. Disease-free survival (DFS) at 15 years was 44% in patients who had a CR to induction chemotherapy, 31% in those who had a partial response (PR), and 7% in those who had less than a PR. There was no improvement in overall survival (OS) or DFS among patients who underwent alternate chemotherapy (MV) compared with those who did not. Using surgery and radiotherapy as opposed to radiotherapy alone as local therapy did not have an impact on the DFS or OS rate. *Conclusion*: These long-term follow-up data show that with a combined-modality approach a significant fraction of patients (28%) remained free of disease beyond 15 years. In contrast, single-modality treatments yielded a DFS of less than 5%. Thus, using combined-modality treatment (chemotherapy, then mastectomy, then chemotherapy and radiotherapy) is recommended as a standard of care for inflammatory breast carcinoma.

Key words Combined-modality treatment · Inflammatory breast carcinoma

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Introduction

Inflammatory breast carcinoma accounts for 1% to 6% of all breast carcinoma in the United States [1]. The long-term disease-free survival (DFS) rates of patients with inflammatory breast carcinoma are very poor with single-modality treatments. Surgery alone (mastectomy) has a very low cure rate; the 5-year overall survival (OS) rate is less than 5%. The overall mean survival after mastectomy alone is 12 to 32 months [2–4]. Radiotherapy alone also results in a low DFS rate [2, 3, 5, 6].

Adding radiation to surgery did not improve the overall survival in the reported studies. Very few patients remained free of disease 5 years after treatment [3, 5].

Because of the poor outcome with any of the single-modality treatments, it is a reasonable approach to treat this disease by combined modality. The most common approach is to begin with two to four cycles of induction chemotherapy. At the completion of induction chemotherapy, an assessment of response is made, and patients are considered for definitive local therapy, such as surgery, radiotherapy, or both. This approach has resulted in tumor shrinkage with down-staging prior to local therapy. The overall response rates to induction chemotherapy have ranged from 33% to 93%, with a mean response rate of 62%. Complete clinical remission has been achieved in 13% of patients after induction chemotherapy. The 5-year DFS rates after combined-modality treatment have ranged from 22% to 48%, with a median survival of 25 to 70 months [3, 4, 7–11].

At M. D. Anderson Cancer Center, since 1973, patients with inflammatory breast carcinoma have been treated using four different combined-modality protocols in prospective studies. All four protocols contained induction chemotherapy: three to four cycles of 5-fluorouracil, doxorubicin, and cyclophosphamide (FAC) with or without vincristine and prednisone (VP). In the first protocol, protocol A, which was started in 1973, patients were treated with FAC, primary radiotherapy, and prolonged maintenance chemotherapy for a total of 2 years. One disadvantage found was that systemic chemotherapy had to be interrupted for up to 10 weeks for radiotherapy [7]. To reduce the prolonged delay between the primary therapy and reinstitution of chemotherapy, in 1978, protocol B was initiated with mastectomy as the primary local therapy. Radiotherapy was given after completion of nine cycles of FAC [8, 12]. In 1982, to improve the response rate, protocol C was initiated, adding VP to FAC [8]. In 1987, protocol D was initiated, which involved using an alternate chemotherapy regimen, methotrexate and vinblastine (MV), after surgery to improve the outcome of patients who did not have a complete response (CR) to induction chemotherapy. The intention was to use chemotherapeutic agents to which patients had not been exposed to achieve the benefit of a noncross resistant mechanism.

In this report, the updated results of the 20 years of experience with these four patient groups are presented to illustrate the durable long-term DFS attainable from a combined-modality approach.

Patients and methods

Patients

Between May 1973 and September 1993, 178 previously untreated patients with biopsy-proven inflammatory breast carcinoma and accompanying inflammatory signs (erythema, peau d'orange, ridging) without distant metastasis were treated at M. D. Anderson Cancer Center. All patients were discussed and examined by a multidisciplinary group of physicians that included medical oncologists, surgeons, and radiation therapists. Staging workup included a complete history and physical examination, blood chemistry analysis, complete blood count with differential, platelet counts, electrocardiogram, mammogram, liver ultrasound or abdominal computed tomography (CT), chest X-radiograph, and bone scans. Head CT scan, bone marrow biopsy and aspiration, and radiographic bone survey were performed only when clinically indicated.

Treatment

The patients were treated in four studies (Table 1).

Protocol A

From 1974 to 1977, 40 patients received three to four cycles of FAC induction chemotherapy prior to radiotherapy. The chemotherapy dosage included 500 mg/m^2 5-fluorouracil given i.v. on days 1 and 8, 50 mg/m^2 doxorubicin given by i.v. rapid infusion on day 1, and 500 mg/m^2 cyclophosphamide given i.v. on day 1 of each 21-day cycle (Table 2). In addition, bacillus Calmette-Guérin (BCG) was given by scarification. After radiotherapy, FAC was continued until a total dose of 450 mg/m^2 doxorubicin had been reached, then maintenance therapy with cyclophosphamide, methotrexate, and

Table 1 Treatment schemes (*CMF* cyclophosphamide, methotrexate, and 5-fluorouracil; *FAC* 5-fluorouracil, doxorubicin, and cyclophosphamide; *FACVP* FAC + vincristine and prednisone; *MV* methotrexate, vinblastine, and folinic acid, *NC* no change; *XRT* radiotherapy)

Protocol	Induction chemotherapy	Local therapy	Adjuvant chemotherapy	Adjuvant radiotherapy
A	FAC × 3–4 cycles	Radiotherapy	FAC, then CMF	No
B	FAC × 3 cycles	Mastectomy	FAC × 6 cycles	Yes
C	FACVP × 3 cycles	Mastectomy	FACVP × 6 cycles	Yes
D	FACVP × 3–4 cycles	Depending on the clinical response to induction chemotherapy: CR: Mastectomy, then FACVP × 8, then XRT PR: Mastectomy, then FACVP × 8, then MV × 6, then XRT < PR: MV × 2; if CR or PR after MV, mastectomy, then MV × 4, then XRT; if NC or PD: after MV, XRT, then mastectomy, if feasible PD: XRT, then mastectomy, then MV × 6, if feasible		

Table 2 Chemotherapy doses and schedules

Drugs	Dose	Timing of administration
FAC		
5-Fluorouracil i.v.	500 mg/m^2	Days 1 and 8
Doxorubicin i.v.	50 mg/m^2	Rapid infusion (protocol A); continuous infusion days 1 to 3 (other protocols)
Cyclophosphamide i.v.	500 mg/m^2	Day 1
FACVP		
FAC	(see above)	(see above)
Vincristine i.v.	1.4 mg/m^2	Day 1
Prednisone orally	40 mg/m^2	Days 1 and 5
MV		
Methotrexate i.v.	75 mg/m^2	Day 1
Vinblastine i.v.	1.7 mg/m^2/day	Continuous infusion days 1 to 5
Folinic acid orally	8 mg	Every 6 h × 6 doses after methotrexate

5-fluorouracil (CMF) was given for a total of 24 months. The maintenance program consisted of 500 mg/m^2 5-fluorouracil given orally on days 1 and 8, 30 mg/m^2 methotrexate given i.m. on days 1 and 8, and 500 mg/m^2 cyclophosphamide given orally on day 2.

Protocol B

From 1978 to 1981, tumor vaccine was added to BCG in 23 patients after three cycles of induction chemotherapy (FAC) followed by mastectomy. Within 10 to 14 days after mastectomy, adjuvant chemotherapy (FAC) was given until a total dose of 450 mg/m^2 doxorubicin had been reached. Maintenance chemotherapy with CMF as given in protocol A was discontinued. All patients received comprehensive radiotherapy after adjuvant chemotherapy.

Protocol C

In 1982, the chemotherapeutic regimens were modified and the route of administration of doxorubicin was changed to continuous infusion over 48 h. Vincristine given at 1.4 mg/m^2 (maximal dose of 2 mg/m^2 in patients less than 50 years of age and 1.5 mg/m^2 in patients 50 years and older) on day 1 and 40 mg prednisone given orally on days 1 to 5 were added to the FAC regimen (FACVP). The maximum cumulative doxorubicin dose in this group was 550 mg/m^2. Between 1982 and 1987, 43 patients were treated with this protocol.

Protocol D

From 1987 to 1993, 72 patients received three to four cycles of FACVP as induction chemotherapy. Response categories were assigned after completion of induction chemotherapy. Complete response (CR) was defined as the complete disappearance of all measurable disease, assessable disease, and all of the signs and symptoms of disease. Partial response (PR) was defined as a more than 50% decrease in the size of the measurable tumor. Less than PR was defined as no evidence of a PR or CR but no progressive disease (PD). PD was defined as a more than 25% increase in the size of measurable tumor. Patients with clinical CR underwent surgery, then received eight cycles of adjuvant chemotherapy (FACVP) and radiotherapy. All patients with other than a CR received 75 mg/m^2 methotrexate i.v. on day 1 and 1.7 mg/m^2 per day vinblastine by continuous infusion over 24 h daily on days 1 to 5 (MV) as follows. Calcium leucovorin (8 mg/m^2) was given orally every 6 h for eight doses starting 24 h after methotrexate. Patients with PR underwent surgery, then received adjuvant chemotherapy (eight cycles of FACVP, six cycles of MV) and radiotherapy. Patients with less than PR received two cycles of MV, then clinical response was again assessed. Those who had PR or CR to MV underwent surgery and then received four cycles of MV and radiotherapy. Those who had no change (NC) or PD after MV received radiotherapy, then surgery if feasible. Patients with PD while receiving FACVP received radiotherapy prior to mastectomy, then received the MV regimen if feasible. Patients were considered treatment failures if they could not complete the planned treatment.

Radiotherapy

Primary radiotherapy with cobalt-60 and electrons consisted of an accelerated twice-daily fractionation schedule delivered to the breast and surrounding lymphatics. In patients whose breast remained intact, 51 Gy in 40 fractions was delivered to the breast over 4 weeks using tangential portals, with each portal being treated daily. A 51-Gy tumor dose was given over 20 days to the supraclavicular and internal mammary nodes. A tangential compression boost, consisting of a 20-Gy tumor dose divided into 16 fractions, was given over 8 days to the entire breast, including the skin but not the rib cage. In protocol A, oppositional boosts were delivered in twice-daily fractions to any clinically positive nodal areas. Accelerated consolidation radiotherapy following mastectomy consisted of 45 Gy given over 3 weeks in 30 fractions using cobalt-60 and electrons. In addition, in patients who underwent mastectomy (protocols B–D), 5 to 15 Gy was delivered to the chest wall scar and to any palpable residual nodes.

Surgery

Between 1978 and 1981 (group B), of 22 patients treated with mastectomy, 4 underwent simple mastectomy and 18 underwent extended simple mastectomy, which include the ipsilateral lower axillary contents (level I). Between 1982 and 1987 (group C), 28 patients underwent extended simple mastectomy and 14 patients had modified radical mastectomies. Between 1987 and 1993 (group D), 56 patients underwent modified radical mastectomy and 11 patients had extended simple lumpectomy. Of 5 patients who did not undergo surgery, 4 had a poor response to induction chemotherapy and their tumors did not become resectable, and 1 refused further treatment after induction chemotherapy. In each of protocols A to C, one patient did not undergo surgery because of PD after three cycles of chemotherapy.

Statistical methods

The DFS and OS rates were calculated according to the method of Kaplan and Meier [13]. Gehan's modification of the generalized Wilcoxon test [14] was used to evaluate the differences among the distributions. *P*-values of 0.05 or less were considered highly statistically significant and strong statistical evidence against the null hypothesis. All data were updated through July 1995.

Table 3 Patient characteristics

Characteristic	No. of Patients (%)				
	Protocol A	Protocol B	Protocol C	Protocol D	Total
Total no. enrolled	40	23	43	72	178
Age (years)					
< 50	15 (38)	14 (61)	17 (40)	32 (44)	78 (44)
≥ 50	25 (63)	9 (39)	26 (60)	40 (56)	100 (56)
Menopausal status					
Premenopausal	11 (28)	14 (61)	16 (37)	29 (40)	70 (39)
Peri- or postmenopausal or ablation by surgery	29 (73)	9 (39)	27 (63)	43 (60)	108 (61)
Mass on mammogram					
Yes	12 (30)	9 (39)	18 (42)	43 (60)	82 (46)
No	22 (55)	12 (52)	24 (56)	29 (40)	87 (49)
Unknown	6 (15)	2 (9)	1 (2)	0 (0)	9 (5)
Skin involvement					
Yes	12 (30)	9 (39)	25 (58)	23 (32)	69 (39)
No	9 (23)	6 (26)	15 (35)	23 (32)	53 (30)
Unknown	19 (48)	8 (35)	3 (7)	26 (36)	56 (31)
Lymphatic invasion					
Yes	14 (35)	13 (57)	22 (51)	50 (69)	99 (56)
No	5 (13)	3 (13)	2 (5)	21 (29)	31 (17)
Unknown	21 (53)	7 (30)	19 (44)	1 (1)	48 (27)
Estrogen receptors					
Positive	2 (5)	6 (26)	10 (23)	22 (31)	40 (22)
Negative	0 (0)	8 (35)	20 (47)	30 (42)	58 (33)
Unknown	38 (95)	9 (39)	13 (30)	20 (28)	80 (45)
Race					
White	35 (88)	18 (78)	35 (81)	55 (76)	143 (80)
Black	1 (3)	3 (13)	4 (9)	6 (8)	14 (8)
Hispanic and others	4 (10)	2 (9)	4 (9)	11 (15)	21 (12)

Results

Patients

Pretreatment characteristics of 178 patients treated from 1973 to 1993 are shown in Table 3. The median follow-up of live patients was 215 months in group A, 186 months in group B, 116 months in group C, and 45 months in group D. The median follow-up of the entire group was 89 months. The median age of the patients on the four protocols was 51 years (range 27–78 years), and 78 patients (44%) were less than 50 years old. There were 70 premenopausal patients (39%). All but 8 patients had stage IIID disease according to the TNM staging system, based on the finding of the inflammatory component of the breast cancer. Eight patients were classified as stage IVA because of supraclavicular lymph node involvement. None of the patients had distant metastases. There were 82 patients (46%) with a vague mass detected on their mammogram, 99 patients (56%) with pathological evidence of lymphatic invasion and 69 (39%) with skin involvement. There were 143 white patients (80%) and 35 black and Hispanic patients (20%). Estrogen receptors were positive in 40 patients (22%), but most were weakly positive. There were no data on hormonal status available for 80 patients (45%).

Survival rates

The DFS and OS rates for all 178 patients with inflammatory breast carcinoma are shown in Fig. 1. Of

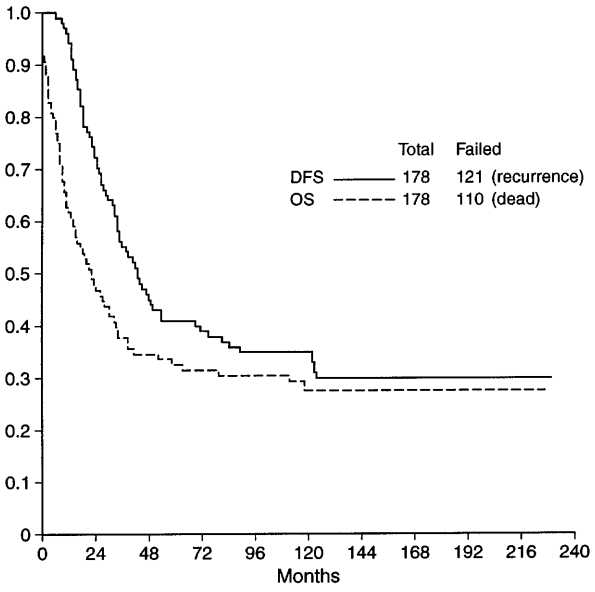


Fig. 1 DFS and OS rates for all 178 patients with inflammatory carcinoma of the breast. (dead NED censored) Total Failed

the 178 patients, 56 were alive at the time of this analysis, 50 (28%) without breast cancer. Among the 50 patients, 5 had a resection of recurrent tumor. Twelve patients died of intercurrent illness without any evidence of recurrence of disease (3 atherosclerotic heart disease, 3 myocardial infarction, 1 congestive heart failure, 1 cerebral vascular accident, 1 chronic obstructive pulmonary disease, 1 hepatic failure, 1 other neoplastic disease, and 1 unknown). The curve showed that there were virtually no recurrences after 10 years. Estimated DFS at 15 years was 28% (SE 5%), at 10 years was 28% (SE 4%), and at 5 years was 32% (SE 4%). Estimated OS at 15 years was 29% (SE 5%), at 10 years was 33% (SE 4%), and at 5 years was 40% (SE 4%). The overall median survival was 37 months. Median survivals were 38 months for protocol A, 38 months for protocol B, 64 months for protocol C, and 34 months for protocol D. Estimated 5-year DFS for protocol A was 32% (SE 7.5%), for protocol B was 22% (SE 8.6%), for protocol C was 37% (SE 7.4%), and for protocol D was 28% (SE 7%). There were no significant differences in the DFS ($P = 0.475$) or OS ($P = 0.820$) among the four different protocols (Fig. 2).

Response to induction chemotherapy

A total of 172 patients received induction chemotherapy as specified by the protocols; 6 patients (3%) had surgery prior to coming to M. D. Anderson Cancer Center and received chemotherapy after surgery. After induction chemotherapy, 127 patients (74%) achieved a major objective tumor response (CR or PR), including 21 patients (12%) with clinical CR (Table 4). Four patients (2%) had PD during induction chemotherapy. After induction chemotherapy, 41 patients (23%) had less than PR or stable disease. After completing combined-modality treatment, 158 (92%) of the patients were rendered free of disease. The remaining 14 patients (8%) had persistent disease; all died with disease except one patient who remained alive with disease at the time of analysis.

Estimated 15-year DFS ($P < 0.001$) was 44% (SE 15%) for patients who had a CR to induction chemotherapy, 31% (SE 6%) for those who had a PR, and 7%

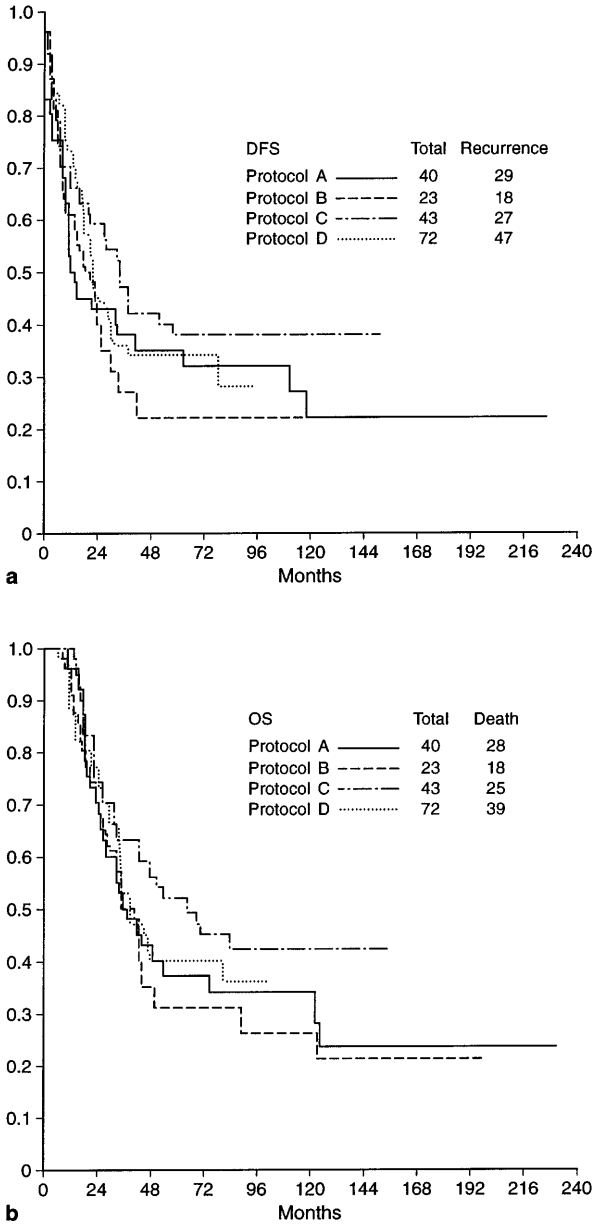
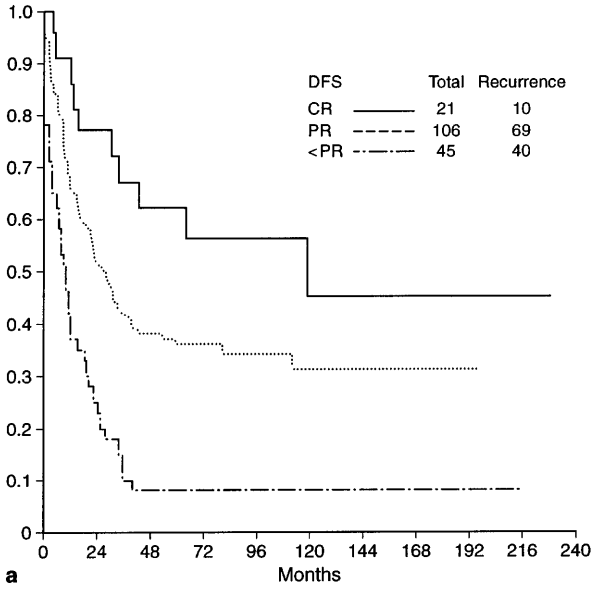


Fig. 2a,b DFS (**a**) and OS (**b**) rates of patients with inflammatory carcinoma of the breast by protocol. There was no significant difference between the protocols in OS ($P = 0.820$) or DFS ($P = 0.4$) rates

Table 4 Response to initial chemotherapy by protocol

Response	No. of patients (%)				
	Protocol A	Protocol B	Protocol C	Protocol D	Total
CR	6 (15)	3 (13)	3 (7)	9 (13)	21 (12)
PR	26 (65)	10 (43)	25 (58)	45 (63)	106 (60)
< PR	7 (18)	8 (35)	11 (26)	15 (21)	41 (23)
PD	1 (3)	2 (9)	0	1 (1)	4 (2)
N/A[a]	0	0	4 (9)	2 (3)	6 (3)
Total	40	23	43	72	178

[a] *N/A* not applicable (history of prior surgery)



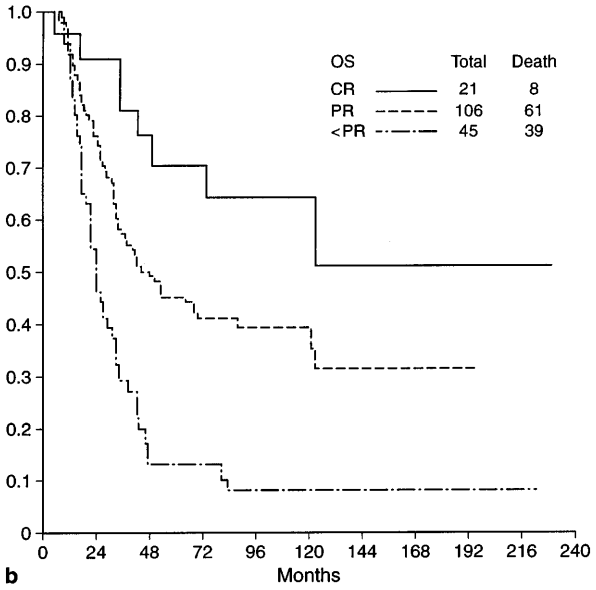


Fig. 3a,b DFS (**a**) and OS (**b**) rates of all patients with inflammatory carcinoma of the breast by initial response to induction chemotherapy. Both DFS and OS rates differed significantly ($P < 0.001$) depending on the initial response to chemotherapy

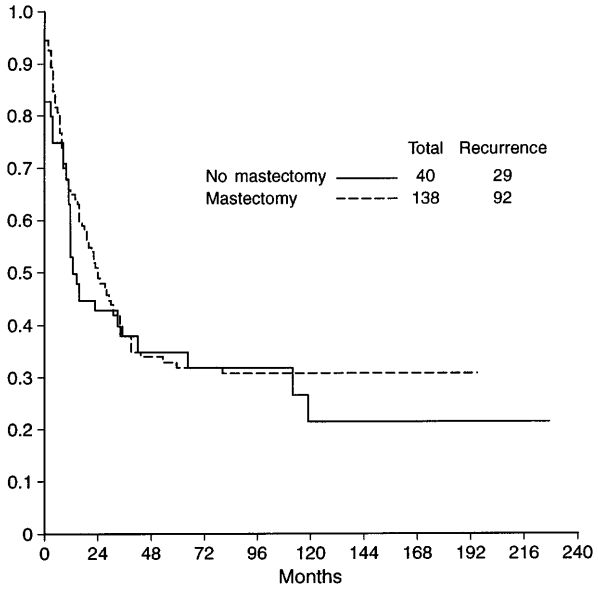


Fig. 4 DFS rates of all patients with inflammatory carcinoma of the breast by local therapy (no mastectomy vs mastectomy). There was no difference in DFS by type of local therapy ($P = 0.418$)

(SE 4%) for those who had less than a PR. Estimated 15-year OS ($P < 0.001$) was 51% (SE 16%) for patients who had a CR to induction chemotherapy, 31% for those who had a PR, and 7% (SE 5%) for those who had less than a PR (Fig. 3).

Of the 178 patients, 63 received FAC and 115 received FACVP. There was no difference in the tumor response rate between patients who received FAC and those who received FACVP: 69% vs 70%. There was no difference in estimated DFS ($P = 0.358$) at 15 years between patients who received FAC and those who received FACVP: 22% (SE 6%) vs 32% (SE 5%). There was also no difference in DFS ($P = 0.418$) by type of local therapy, radiation alone vs surgery and radiation (Fig. 4).

Initial pattern of treatment failure

Among the 178 patients, 121 (68%) had a recurrence of breast cancer: 35 (20%) had locoregional recurrence, 70 (39%) had systemic recurrence, and 16 (9%) had central

Table 5 Pattern of initial treatment failure

	No. of patients (%)				
	Protocol A	Protocol B	Protocol C	Protocol D	Total
Total patients (%)	40	23	43	72	178
Recurrences					
Locoregional	7 (18)	6 (26)	6 (14)	16 (22)	35 (20)
Systemic	17 (43)	11 (48)	19 (44)	23 (32)	70 (39)
Central nervous system	5 (13)	1 (4)	2 (5)	8 (11)	16 (9)
Total	29 (73)	18 (78)	27 (63)	47 (65)	121 (68)

nervous system relapse. The pattern of treatment failure did not differ between protocols (Table 5). Among those with systemic recurrence, 22 patients (12%) had bone metastases, 17 (10%) had liver metastases, 10 (6%) had lung metastases, 7 (4%) had nodal metastases, and 7 (4%) had pleural metastases. Among those with locoregional recurrence, 18 (10%) had chest wall metastases, 7 (4%) had ipsilateral metastases, and 4 (2%) had contralateral metastases.

Prognostic factors

There were no significant differences in DFS ($P = 0.250$) and OS rates between those less than 50 years of age and those 50 years of age and above (Fig. 5). The estimated 15-year DFS rate at age less than 50 years was 26% and at age 50 years and above was 27%.

Toxicity

Nine patients (5%) had cardiac toxic effects from doxorubicin, 5 (13%) on protocol A, 2 (9%) on protocol B, and 2 (3%) on protocol D. Eight patients had congestive heart failure and one patient had arrhythmia.

Response to alternate chemotherapy

In protocol D, the role of alternate chemotherapy was evaluated among patients who had less than a CR to induction chemotherapy. Nine patients had a CR, 45 patients had a PR, 15 patients had less than a PR, and 1 patient had PD (Table 6). Surgery was performed on 67 patients (Table 6). A total of 43 patients then received alternate chemotherapy. There was no significant difference in DFS ($P = 0.289$) or OS ($P = 0.589$) at 5 years between patients who received alternate chemotherapy and those who did not. DFS at 5 years was 30% (SE 9%) among patients who did not receive alternate chemotherapy and 38% (SE 9%) among those who received alternate chemotherapy (Fig. 6).

Table 6 Results of protocol D

Response/treatment	No. of patients		
	Total	Alive	Recurrence
CR			
MV	3	2	1
No MV	6	4	2
Total	9	6	3
PR			
MV	24	13	11
No MV	21	7	15
Total	45	20	26
< PR			
MV	14	2	12
No MV	1	0	1
Total	15	2	13
PD			
MV	1	0	1
No MV	0	0	0
Total	1	0	1
Off protocol			
MV	1	0	1
No MV	1	0	0
Total	2	0	1

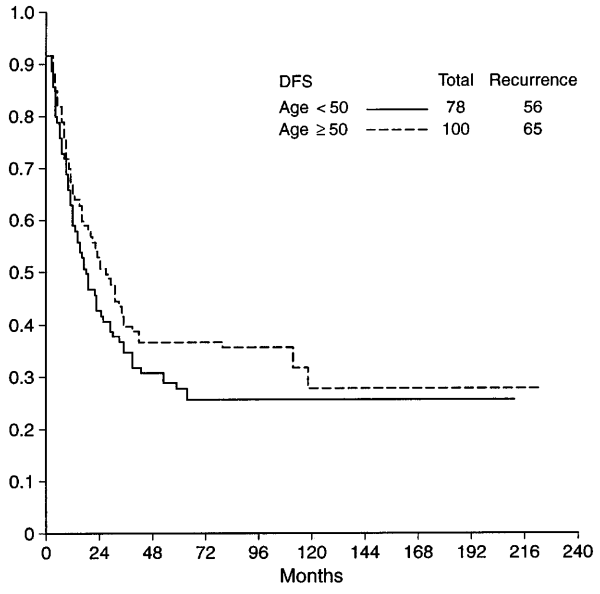


Fig. 5 DFS rates of patients with inflammatory carcinoma of the breast by age. There was no difference in DFS rates between patients < 50 years and patients ≥ 50 years ($P = 0.250$)

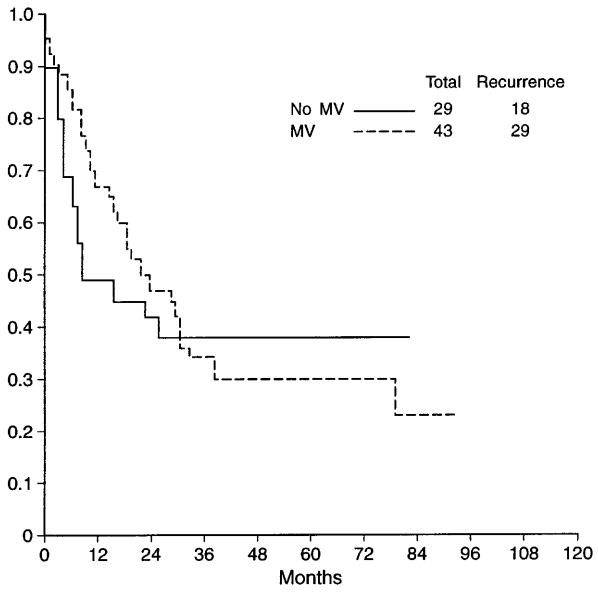


Fig. 6 DFS rates of patients with inflammatory carcinoma of the breast on protocol D by whether alternate chemotherapy was given. The DFS rate for patients who received MV and for those who did not receive MV did not differ significantly ($P = 0.289$)

Among the nine patients who had a clinical CR, six received eight cycles of FACVP as adjuvant chemotherapy. The other three received an additional three cycles of MV after FACVP because of poor pathological response after induction chemotherapy. Among the 45 patients who had a clinical PR, 24 actually received both FACVP and MV as planned, and 21 did not complete the MV after the FACVP regimen. Of these patients, 10 recurred while receiving FACVP, 1 recurred before receiving FACVP, 1 had an infectious complication, and 1 was registered on another protocol for high-dose chemotherapy with bone marrow transplantation. Eight patients did not receive any MV after FACVP. Four of these patients were in pathological CR even though clinically patients were considered to have had a PR after induction chemotherapy. Of patients who had less than a PR, 14 received MV as scheduled. However, no patients had a CR to MV, only 4 had a PR to MV, and 7 had PD or NC. All four patients with PR underwent surgery, but all had rapid recurrence of disease. The other three patients received local therapy after the induction chemotherapy, then received MV as an adjuvant chemotherapy.

We analyzed the results for patients on protocol D from different aspects to see if non-cross-resistant chemotherapy with MV had any impact on overall outcome among poor-prognosis patients who had less than a PR but it did not show any improvement. Analysis based on pathological response after induction chemotherapy did not show any improvement in the DFS or OS rates compared to the FACVP protocol. Analysis was also conducted based on lymph node status after induction chemotherapy (fewer than four nodes involved vs more than four nodes involved). However, there were still no significant differences in DFS or OS rates between protocol D and earlier studies.

Discussion

We present here the long-term follow-up data of patients with inflammatory breast carcinoma treated with a combined-modality approach. Local modalities alone – surgery, radiotherapy, or surgery and radiotherapy – achieve less than a 5% long-term DFS rate among patients with inflammatory breast carcinoma. Since induction chemotherapy protocols were initiated in 1973 at M. D. Anderson, an estimated 28% of patients have been alive and free of disease at 15 years. We did not observe any recurrences after 10 years. This experience confirms that a significant fraction of patients remained free of disease at the time of analysis using this treatment approach.

The most important prognostic factor was the response to induction chemotherapy. There was a 44% 15-year DFS rate among patients who had a CR to induction chemotherapy. Patients with PR had a 31% DFS rate at 15 years, and those with less than a PR had a 7% DFS rate at 15 years. Other prognostic factors, such as age, estrogen receptor status, and race, did not affect the overall outcome. The status of hormonal receptors has been an important prognostic factor in noninflammatory breast cancer. However, it has been a controversial prognostic factor among patients with inflammatory breast cancer [15]. Among those patients with known hormonal receptor status, 40% were positive for estrogen receptor. There was no difference in DFS rate between positive and negative patients. Most patients had a very weak positivity. Therefore, tamoxifen, which is more likely to benefit patients with positive estrogen receptor, may not benefit these patients.

The locoregional recurrence rate, as in previous studies, was less than 20%, probably because of radiotherapy. The pattern of local failure did not differ by type of local therapy. However, we recommend mastectomy as a local therapy because it will result in debulking the large amount of tumor, there is less concern about residual tumor, there is a smaller amount of radiation dosage delivery, and adjuvant chemotherapy can be reinstituted more quickly than after radiotherapy.

The addition of vincristine and prednisone to FAC chemotherapy did not improve the long-term outcome significantly. In protocol D, alternate chemotherapy was employed after adjuvant FACVP for patients who had less than a PR. However, it did not result in an improvement in the overall outcome. Rapid recurrence of disease while patients were receiving adjuvant FACVP before they received alternate chemotherapy (MV) made this a poor approach. An early change to alternate chemotherapy after surgery needs to be considered for patients who have a PR or less than a PR. We will also need to investigate new chemotherapeutic agents, such as paclitaxel or navelbine, and dose intensification, including high-dose chemotherapy with autologous transplantation, to improve the tumor response rate for patients who have poor prognostic features.

There was a discrepancy between assessment of clinical response and assessment of pathological response, which resulted in participating physicians treating patients differently in protocol D; this may have affected our outcome. In future investigations we may employ pathological response as a criterion for further treatment planning.

The use of combined-modality treatment in patients with inflammatory breast carcinoma is now an established practice that gives durable DFS beyond 15 years in a significant fraction of patients. Therefore, we recommend induction chemotherapy with three to four cycles of FAC, then proceeding with surgical resection and axillary lymph node dissection, then six to eight cycles of adjuvant FAC chemotherapy, and consolidating with radiotherapy.

Complete response to induction chemotherapy is an important prognostic factor for long-term DFS and OS. Obtaining a higher CR by improving standard dose induction chemotherapy or by dose intensification should be investigated. Also, the use of other chemotherapy regimens after surgery for patients who do not achieve a CR needs to be evaluated.

References

1. Levine PH, Steinhorn SC, Ries LG, et al (1985) Inflammatory breast cancer: The experience of the Surveillance, Epidemiology, and End Results (SEER) program. J Natl Cancer Inst 74: 291–27
2. Hagelberg RS, Jolly PC, Anderson RP (1984) Role of surgery in the treatment of inflammatory breast carcinoma. Am J Surg 148: 125–131
3. Jaiyesimi IA, Buzdar AU, Hortobagyi G (1992) Inflammatory breast cancer: a review. J Clin Oncol 10: 1014–1024
4. Singletary SE, Ames FC, Buzdar AU (1994) Management of inflammatory breast cancer. World J Surg 18: 87–92
5. Perez CA, Fields JN (1987) Role of radiation therapy for locally advanced and inflammatory carcinoma of the breast [published erratum appears in Oncology (Huntingt); July 1: 19 1987]. Oncology (Huntingt) 1: 81–94
6. Lamb CC, Eberlein TJ, Parker LM, et al (1991) Results of radical radiotherapy for inflammatory breast cancer. Am J Surg 162: 236–242
7. Fein DA, Mendenhall NP, Marsh RD, et al (1994) Results of multimodality therapy for inflammatory breast cancer: an analysis of clinical and treatment factors affecting outcome. Am Surg 60: 220–225
8. Koh EH, Buzdar AU, Ames FC, et al (1990) Inflammatory carcinoma of the breast: results of a combined-modality approach – M.D. Anderson Cancer Center experience. Cancer Chemother Pharmacol 27: 94–100
9. Fields JN, Kuske RR, Perez CA, et al (1989) Prognostic factors in inflammatory breast cancer. Univariate and multivariate analysis. Cancer 63: 1225–1232
10. Swain SM, Lippman ME (1989) Treatment of patients with inflammatory breast cancer. Important Adv Oncol: 129–150
11. Thoms WJ, McNeese MD, Fletcher GH, et al (1989) Multimodal treatment for inflammatory breast cancer. Int J Radiat Oncol Biol Phys 17: 739–745
12. Fastenberg NA, Martin RG, Buzdar AU, et al (1985) Management of inflammatory carcinoma of the breast. A combined modality approach. Am J Clin Oncol 8: 134–141
13. Kaplan El, Meier P (1958) Nonparametric estimation from incomplete observations. J Am Stat Assoc 53: 457–481
14. Gehan EA (1965) A generalized Wilcoxon test for comparing arbitrarily singly-censored sample. Biometrika 52: 203–224
15. Paradiso A, Tommasi S, Brandi M, et al (1989) Cell kinetics and hormonal receptor status in inflammatory breast carcinoma. Comparison with locally advanced disease. Cancer 64: 1922–1927