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Original article

Primary (neoadjuvant) chemotherapy and radiotherapy compared with primary radiotherapy alone in stage IIb-IIIa breast cancer

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Summary

Background: A phase III randomized trial was activated to evaluate the efficacy of preoperative combined chemotherapy and radiotherapy as compared to preoperative radiation therapy alone, in patients with breast cancer presenting with a clinical stage of IIb-IIIa (TNM classification).

Patients and methods: From 1985 to 1990, 271 patients, aged 27–55 years, with stage IIb-IIIa breast cancer were randomized to receive either one or two courses of thiotepa 20 mg (i.m. injection) on the days 1, 3, 5, 7, 9, 11 (total dose per course 120 mg), methotrexate 40 mg/m^2, i.v. on days 1 and 8, and 5-fluorouracil 500 mg/m^2, i.v. on days 1 and 8 (TMF regimen) plus radiotherapy (Group I, 137 patients), or preoperative radiation therapy only (Group II, 134 patients). After the preoperative treatment all patients underwent mastectomy and complete axillary clearance, and then received 4–6 courses of TMF. The trial was conducted in a single institution (N. N. Petrov Research Institute of Oncology, St. Petersburg).

Results: Histopathological assessment of the mastectomy specimens showed complete regression of the tumour in 29.1% of the patients in group I and in 19.4% of the patients e.c. in group II. The estimated 5-year overall survival percentages were 86.1% for group I, and 78.3% for group II ($P > 0.05$). 5-year disease-free survival percentages were 81.0% and 71.6%, respectively ($p < 0.05$).

Conclusions: Despite the low number of the patients included in the trial, we were able to detect a significant improvement in treatment results with a combination of chemotherapy and radiation therapy given prior to mastectomy over those of local therapy alone with radiation therapy followed by mastectomy, for average- and high-risk patients with operable breast cancer.

Key words: neoadjuvant chemotherapy, radiotherapy, breast cancer

Introduction

The aim of neoadjuvant (preoperative) chemotherapy is to decrease the size of primary tumours and reduce the systemic dissemination of micrometastatic disease, before appropriate surgical treatment. This should lead to improved local control of the disease as well as improved survival. A meta-analysis of all randomized trials of adjuvant chemotherapy in operable breast cancer showed a significant reduction of mortality ranging between 25% and 30% [1]. The trials included in this meta-analysis had studied only postoperative systemic adjuvant therapies.

Administration of adjuvant systemic chemotherapy already during surgery in patients with operable disease, or preoperatively as primary therapy, is under investigation. Stage IIIa breast cancer, for which in most cases primary surgery is not appropriate, has been treated for several years with either radiotherapy or chemotherapy in combination with radiotherapy.

In recent years, interest in the use of combined chemotherapy and radiation therapy for breast cancer has increased. It has been proven that both radiotherapy and chemotherapy lead to the death of stem cells in normal tissue as well as in rapidly proliferating tissues. Much less is known about the processes resulting from chemo- and radiotherapy is slowly proliferating cells, but an enhancement of the cytotoxic effect in these tissues upon the simultaneous application of the two therapies has been shown [2].

We present the results of a randomized clinical trial, in which the experimental treatment consisted of primary (neoadjuvant) chemotherapy in combination with radiotherapy.

Materials and methods

Two hundred seventy-one breast cancer patients stage IIb-IIIa (TNM-classification, 4th edition) aged 27 to 55 years were included in the trial from January 1985 to January 1990 (Table 1). The patients were randomized to receive either neoadjuvant chemotherapy in combination with preoperative radiotherapy (Group I, 137 patients), or preoperative radiotherapy alone (group II, 134 patients). Randomisation was performed using a Table of random numbers. The study design is illustrated in Fig. 1. The diagnosis of breast cancer was based upon a cytological examination of cells obtained in all patients by means of fine needle biopsy (FNA).

Table 1. Patients recruited into study.

	Mastectomy + adjuvant chemotherapy	
	Group I. Neoadjuvant chemotherapy + preoperative radiotherapy	Group II. Preoperative radiotherapy
Number of patients	137	134
Age	27–55	29–55
Average age	49.7	51.2
Stage (TNM)		
T2N1M0	18 (13.1%)	16 (11.9%)
T3N0M0	41 (29.9%)	43 (32.0%)
T1-2N2M0	7 (5.1%)	7 (5.2%)
T3N1M0	71 (51.8%)	68 (50.7%)
Number of cycles of TMF chemotherapy (neoadjuvant + adjuvant in Group I, adjuvant in Group II)		
6	72 (52.5%)	78 (58.2%)
5	30 (21.8%)	25 (18.6%)
4	19 (13.8%)	24 (17.9%)
3 and less	16 (11.9%)	7 (5.2%)

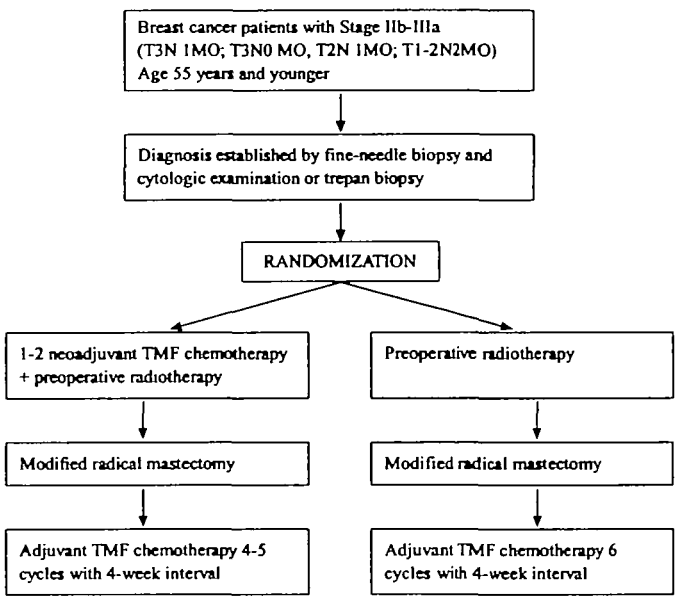

Fig. 1. Design of clinical trials of neoadjuvant chemotherapy in breast cancer patients with stage IIb-IIIa in N. N. Petrov Research Institute of Oncology (St. Petersburg, 1985–1990).

Preoperative radiotherapy was performed in both groups using a 'Rokus' apparatus (Cobalt-60). The mammary gland was irradiated daily through tangential fields, foci single dose 2 Gy, total dose 60 Gy. The axillary area was also irradiated (total dose 40 Gy). Supraclavicular and subclavicular areas were irradiated with single daily doses of 2 Gy (total dose 40 Gy).

A modified radical mastectomy (including complete axillary dissection) was performed in all patients 3–4 weeks after completion of radiation therapy.

The patients allocated to group I received 1–2 cycles of TMF combination chemotherapy consisting of thiotepa 20 mg i.m., on days 1, 3, 5, 7, 9, 11 (120 mg total dose/cycle), methotrexate, 40 mg/m^2, i.v. on days 1 and 8, and 5-fluorouracil, 500 mg/m^2, i.v. on days 1 and 8. Chemotherapy was started before and continued during radiation therapy.

Ninety-four of the 137 (68.8%) patients in group I received one cycle of TMF chemotherapy in the preoperative period, and 43 patients (31.2%) received two. The decision to give the second course of TNF was based upon the observation of a limited response of either the primary tumour or of the metastatic axillary lymph nodes to the first cycle of chemotherapy.

After the surgery, the patients in both groups received 4–6 cycles of combined adjuvant chemotherapy of the same TMF combination administered every 4–6 weeks (Table 1), starting during mastectomy.

Careful macroscopic and microscopic examination of the mastectomy specimens was carried out. Twenty or more sections from the site of the primary tumour were examined by the pathologist. The tumour area was determined according to mammographical data and by the marking of the mastectomy specimen performed by the surgeon during the macroscopic examination. In instances of complete regression of the primary tumour, the typical changes related to scar formation were looked for. Sections of the other quadrants of the breast and the subareolar region were also examined, in addition to at least twelve axillary lymph nodes.

Response to treatment was assessed by means of palpation, dynamic mammography (2 weeks after the radiotherapy, and compared with the pre-treatment baseline films). Evaluation of response was done using the standard WHO criteria for advanced breast cancer [3]. Shrinkage of tumour size (largest perpendicular diameters) by less than 50% was evaluated as 'without effect'. Reduction of the size of the tumour and of metastatic lymph nodes of 50% or more was defined as 'partial response'. Complete disappearance of the primary tumour and the lymph node metastases indicated 'complete response'.

Disease-free survival (DFS) and overall survival (OS) estimates were calculated from the date of initial treatment (neoadjuvant chemotherapy for group I and radiation therapy for group II) using the method described by Kaplan and Meier [4]. Tests of significance were carried out using the log rank chi-square technique [5]. All p-values were two-sided.

Results

The results of the trial are presented at a median follow-up time of 53 months. Table 2 displays the treatment results for the preoperative treatment in the two

Table 2. Treatment results.

	Group I. Neoadjuvant chemotherapy + preoperative radiotherapy	Group II. Preoperative radiotherapy
	137 patients	134 patients
Complete response		
a) Clinical examination	17 (12.4%)	8 (5.9%)
b) Mammogram	48 (35.0%)	37 (27.6%)*
Partial response		
a) Clinical examination	78 (56.9%)	69 (51.4%)
b) Mammogram	50 (36.4%)	43 (32.0%)
No effect		
a) Clinical examination	42 (30.6%)	57 (42.5%)*
b) Mammogram	39 (28.4%)	54 (40.2%)

* $P < 0.05$.

groups evaluated by clinical and mammographic means.

Clinically determined complete responses were seen in 12.4% of the group I patients and 5.9% of those in group II. Partial response was similar in the two groups (56.9% and 51.4%, respectively).

Mammographic evaluation showed a higher incidence of complete response in group I than in group II (35.0% and 27.6%, respectively).

Table 3 shows the treatment results by histopathological examination. This revealed greater differences between the two treatment groups. On macroscopic examination, the group treated with TMF chemotherapy in combination with radiotherapy achieved 45.9% complete responses as compared with 31.3% in patients treated with radiation therapy alone. Microscopic examination revealed no traces of the tumour in 40 of 137 patients (29.1%) treated with neoadjuvant chemotherapy + preoperative radiotherapy and in 26 of 134 patients (19.4%) treated with radiotherapy alone.

The effects of treatment upon OS and DFS are depicted in Figs 2 and 3. These show that both were longer for patients receiving neoadjuvant chemotherapy in the preoperative period. The difference in overall survival between the two treatment groups is not statistically significant. The estimated 5-year disease-free survival percentages were 81.0% for group I and 71.6% for group II.

Table 3. Treatment results by pathology examination.

Treatment groups	Number of patients	Complete response	
		Gross examination	Microscopic examination
I. Neoadjuvant chemotherapy + preoperative radiotherapy	137	63 (45.9%)	40 (29.1%)
II. Preoperative radiotherapy	134	42 (31.3%)	26 (19.4%)

$P < 0.05$.

Detailed analysis of survival rates based on the mammographically determined degree of tumour response (Table 4) showed a trend for longer overall and disease-free survivals for complete and partial responders, particularly those in group I. The small number of patients in the subgroups defined by response does not allow any statistical confirmation ($p > 0.05$) of the claim that degree of response is a marker for prolonged survivorship.

Microscopic examination of the mastectomy specimens of 40 of 137 patients (29.1%) who received neoadjuvant chemotherapy revealed no evidence of cancer. Thirty-eight of these 40 patients (95.0%) were alive 5 years after surgery. Two patients (5%) died of distant metastases. Of the remaining 97 patients with microscopical evidence of residual tumour, 73 (75.2%) were alive 5 years after surgery with no evidence of disease. Twenty-four patients (24.7%) relapsed, and 17 of these died of distant metastases.

The TMF combination chemotherapy was fairly well

Table 4. 5-year survival according to response measure on mammography.

Degree of tumour regression	Complete response	Partial response	No effect
Mastectomy + adjuvant chemotherapy			
Neoadjuvant chemotherapy + preoperative radiotherapy			
No. of pts	48	50	39
No. of deaths	4	7	8
No. of pts with relapses and metastases	7	9	10
Overall survival %	91.6	86.0	79.4
Disease-free survival %	85.4	82.0	74.3
Preoperative radiotherapy			
No. of pts	37	43	54
No. of deaths	4	11	14
No. of pts with relapses and metastases	8	13	17
Overall survival %	89.1	74.4	74.0
Disease-free survival %	78.3	69.7	68.5

$p > 0.05$.

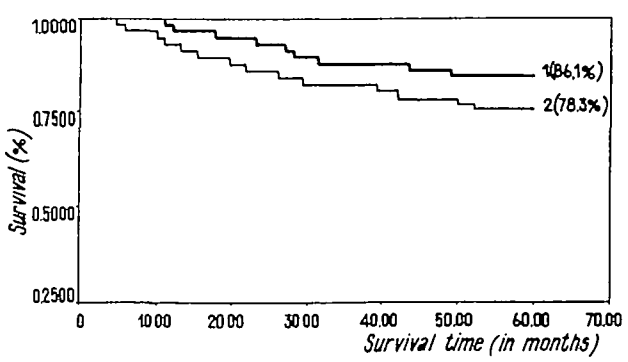

Fig. 2. Overall survival in groups of patients receiving neoadjuvant chemotherapy (1 = 137 patients) and control (2 = 134 patients). $P > 0.05$.

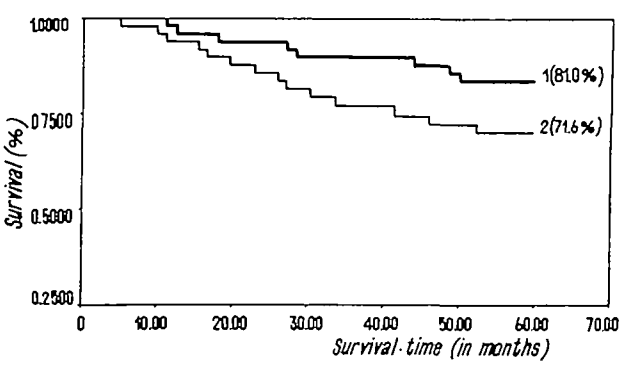

Fig. 3. Disease-free survival in groups of patients receiving neoadjuvant chemotherapy (1 = 137) and control (2 = 134 patients). $P = 0.0442$.

tolerated, with the most frequent toxic complications being leukopenia and thrombocytopenia (Table 5).

Following the third course of adjuvant chemotherapy leukopenia and thrombocytopenia (WBC less than 3×10^9, platelets less than 100,000) were seen for a brief period (1 to 4 weeks) in 78%–80% of patients in group I and 74%–78% of the patients in group II.

Gastrointestinal side effects such as nausea and vomiting were recorded in 62.7% of the patients receiving chemotherapy. Other toxic effects such as stomatitis and gastroenteritis were observed in 5.2% of patients. Among the post-surgical complications was a high incidence of prolonged (3–4 weeks) lymphorrhea, observed in 18.2% of patients receiving neoadjuvant chemotherapy, and in 16.4% of those treated with preoperative radiotherapy alone. Suppuration of the postoperative wound occurred in 4.3% of patients treated with neoadjuvant chemotherapy, and in 6.7% of those treated with preoperative radiotherapy alone. During the postoperative period pneumonia was diagnosed in 2.9% of patients who had received neoadjuvant chemotherapy and in 3.7% of patients treated with preoperative radiotherapy alone.

Discussion

The rate of microscopic complete regression of the tumour was higher after neoadjuvant chemotherapy than after radiotherapy alone (29.1% versus 19.4%).

The incidence of complete regression measured by palpation was considerably lower than when assessed by dynamic mammography or by macroscopic and microscopic examination of the mastectomy specimen. Thus, evaluation of the preoperative treatment effects should take into account that mammographic imaging allows a more precise assessment of response. Furthermore, 5-year DFS after complete tumour regression according to mammography and macroscopic and microscopic examination of the specimen do not markedly differ (85%, 86% and 89%, respectively).

Table 5. Toxic and postoperative complications.

	Mastectomy + adjuvant chemotherapy	
	Group I. Neoadjuvant chemotherapy + preoperative radiotherapy	Group II. Preoperative radiotherapy
	137 patients	134 patients
Hematologic		
Leukopenia		
3000 mm³	110 (80.2%)	104 (77.6%)
2000 mm³	31 (22.6%)	23 (17.1%)
Thrombocytopenia		
150000	107 (78.1%)	99 (73.8%)
50000	27 (19.7%)	23 (17.1%)
Nausea, vomiting	86 (62.7%)	79 (58.9%)
Stomatitis, gastroenterocolitis	8 (5.8%)	7 (5.2%)
Skin allergic reactions and moist epidermitis	9 (6.5%)	12 (8.9%)
Postoperative		
Lymphorrea	25 (18.2%)	22 (16.4%)
Suppuration	6 (4.3%)	8 (6.7%)
Pneumonia	4 (2.9%)	5 (3.7%)

The microscopic complete tumour regression rate is higher (29.1%) than is usually described in the literature [6]. This may be explained by the combined modality approach used in our trial.

The relatively high incidence of local tumour response was not accompanied by a similar substantial prolongation of survival in the neoadjuvant group over that of the radiation therapy-alone group. It may be hypothesized that the effects of the postoperative chemotherapy reduced the difference of ultimate treatment outcome in the two groups.

There is an increasing amount of data on the effectiveness of preoperative and postoperative chemoradiation therapy [7–13]. During the past 20 years most of the oncology centres in Russia have primarily used preoperative radiation therapy for treatment of stages II-III breast cancer because of the relatively rare locoregional recurrences after this type of treatment as compared with postoperative radiation therapy [14, 15]. However, the use of preoperative radiation therapy alone was not accompanied by an increase in overall survival [7, 15]. The data from a number of reports show that the use of neoadjuvant (preoperative) chemotherapy considerably improves the results of treatment of locally advanced breast cancer, and also prolongs the disease-free survival [6, 11, 12].

Preoperative chemotherapy is still a matter of controversy and research. The following pragmatic considerations favour its use:

1. Assessment of the degree of tumour regression after the cytotoxic treatment makes it possible to determine the sensitivity of the malignant cells to the treatment and to establish whether a more aggressive adjuvant therapy might be useful for patients who either did not respond, or whose response was only moderate.
2. Tumour response might allow breast conserving treatment in some of the patients [16].

Our study was carried out using the TMF combination chemotherapy, which is similar to CMF. It is plausible that a neoadjuvant chemotherapy, which includes doxorubicin or epirubicin (FAC, FEC) would be more effective [17]. Trials with preoperative FEC chemotherapy in comparison with postoperative FEC chemotherapy are being carried out within the EORTC program (POCOB Protocol) [18]. In 1988, the NSABP started a clinical trial (B-18) to determine whether preoperative chemotherapy is superior to the same chemotherapy given postoperatively [7, 19]. Results of these trials, which include many more patients than our trial, might provide the ultimate answer to the question of whether

the primary treatment of breast cancer should start with systemic treatments.

References

1. Early Breast Cancer Trialists' Collaborative Group. Systemic treatment of early breast cancer by hormonal, cytotoxic or immune therapy: 133 randomised trials involving 31,000 recurrences and 24,000 deaths among 75,000 women. Lancet 1992; 339: 1–15, 71–85.
2. Howes AE, Coleman CN, Phillips ThL et al. Combined modality therapy using cytotoxic agents and radiation therapy. Am J Clin Oncol 1988; 11: 304–12.
3. Feldman LD, Hortobagyi GN, Buzdar AV et al. Pathological assessment of response to induction chemotherapy in breast cancer. Cancer Res 1986; 46: 2578–81.
4. Bonadonna G, Veronesi U, Brambilla C et al. Primary chemotherapy to avoid mastectomy in tumours with diameters of three centimeters or more. J Natl Cancer Inst 1990; 82: 1539–45.
5. Kaplan EL, Meier P. Nonparametric estimation from incomplete observations. J Am Statist Ass 1958; 53: 457.
6. Peto R, Pike MC, Armitage P et al. Design and analysis of randomized clinical trials requiring prolonged observation of each patient. Br J Cancer 1976; 34: 585–612.
7. Fisher B, Osborne CK, Margolese R et al. In Holland JF, Frei E, Bast RC (eds): Neoplasms of the breast. Cancer Medicine. Leat and Febiger: Philadelphia, London 1993; 2: 1706–74.
8. Sorace RA, Bagley CS, Lichter AS et al. The management of nonmetastatic locally advanced breast cancer using primary induction chemotherapy with hormonal synchronization followed by radiation therapy with or without debulking surgery. World J Surg 1985; 9: 775–81.
9. Mansi JL, SMith IE, Walsh J et al. Primary medical therapy for operable breast cancer. Eur J Cancer Clin Oncol 1989; 25: 1623.
10. Semiglazov VF, Topuzov EE, Bavli YaL et al. Neoadjuvant chemotherapy in complex treatment of breast cancer. Probl Oncol 1992; 38: 936–42.
11. Valagussa R, Zambetti M, Bonadonna G. Surgery in advanced breast cancer. Lancet 1988; 311: 716–7.
12. Hortobagyi GN. Comprehensive management of locally advanced breast cancer. Cancer 1990; 66: 1378–91.
13. Ragaz J, Coldman A, Salinas F et al. Neoadjuvant (preoperative) chemotherapy. In Ariel IM, Cleary JB (eds): Breast cancer. Diagnosis and treatment. McGraw-Hill Book Company: New York 1986; 312–27.
14. Wallgren A, Armer O, Bergstrom J et al. Radiation therapy in operable breast cancer: Results from the Stockholm trial on adjuvant radiotherapy. Int J Radiol Oncol Biol Phys 1989; 12: 533–42.
15. Semiglazov VF, Topuzov EE, Bavli YaL et al. Long-term results of breast cancer treatment. Voprosy Oncologii 1983; 29: 25–30.
16. Hossfeld DU, Sherman CD, Love RR et al. Manual of Clinical Oncology. UICC. Fifth edition. Springer-Verlag: Berlin 1990.
17. Hortobagyi GN. Overview of new treatments for breast cancer. Breast cancer research and treatment 1992; 21: 3–13.
18. Pre-operative chemotherapy in operable breast cancer. (EORTC Protocol 10902). EORTC Newsletter 1992; 1: 1–16.
19. Fisher B, Wickerham DL, Redmond C. Recent developments in the use of systemic adjuvant therapy for the treatment of breast cancer. Semin Oncol 1992; 19: 263–77.

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