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Advanced Breast Cancer: Are the Traditional Stratification Parameters Still of Value When Patients are Treated with Combination Chemotherapy?*

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Abstract—*For many years the results of all studies with hormone therapy and a single agent chemotherapy were correlated to three conventional prognostic parameters: disease-free interval, menopausal status and dominant lesion. These parameters are currently utilized in all trials to stratify patients before randomization. Present analysis was undertaken to verify whether the traditional parameters still bear a meaningful prognostic value when patients are treated with effective combination chemotherapy. This series comprises 318 women who, during the past 8* yr, *were included in controlled studies with 4 drug combinations (CMFV, CMF, AV, AVP). In the whole series CR plus PR was 56.3% and median survival 19* months (*responders 24.5* months, *non-responders 11.5* months). *The rate of response was not statistically affected by the disease-free interval (DFI). However, the median survival of responders was decreased in those with DFI* < 2 yr (19 months) *when compared with DFI simultaneous or* ≧ 2 yr (27–25 months). *The incidence of CR plus PR was significantly decreased in patients* < 2 yr *postmenopausal in comparison to pre- and postmenopausal women* ≧ 2 yr. *Also the median survival was decreased in women whose menopause occurred less than* 2 yr *prior to the start of chemotherapy. No clear-cut difference was detected among the three different categories of dominant disease with the exception of those patients with the concomitant association of visceral (with or without liver), osseous and soft tissue involvement.*

INTRODUCTION

SINCE the beginning of 1950 the results of systemic treatment and primarily endocrine treatment, for advanced breast cancer, were correlated to three conventional prognostic parameters: disease-free interval, menopausal status and site of dominant disease [1]. Long free-interval (> 2 yr), age > 35 yr for ablative endocrine therapy, and > 60 yr for additive endocrine therapy, respectively, soft tissue and bone extent, were all considered as favorable prognistic variables. These traditional categories are currently being utilized in all trials to stratify patients, also when combination chemotherapy is used. Present analysis was undertaken to verify whether the three parameters still bear a meaningful prognostic value after multiple drug regimens and to ascertain whether the administration of effective chemotherapy did alter the prognosis of advanced breast cancer. The analysis will take into consideration the per cent of complete plus partial responders and their median survival.

MATERIALS AND METHODS

Patients selection

A total of 318 consecutive women who, from November 1970 to March 1977 were entered into different controlled studies carried out at the Istituto Nazionale Tumori of Milan, were considered suitable for this analysis. The criteria utilized in our Institute to

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select advanced breast cancer patients eligible for clinical trials are presented in Table 1.

Patients in whom the sole manifestation of the disease was either pleural effusion, or ascites, osteoblastic bone lesions as well as those who presented metastases of the central nervous system were excluded. There must have been evidence of progressive disease at the start of the chemotherapeutic treatment. The performance status must have been at least 50 according to the Karnofsky scale and life expectancy $\geqq 2$ months. Furthermore, a number of informations was required for each patient to properly assess: (a) the stage of primary disease at the time of initial presentation according to the TNM International classification [2]; (b) the extent and date of the treatment of the primary tumor as well as the time of the first treatment failure; (c) dates, agents and results(s) of previous treatment(s) for recurrent or inoperable breast cancer; (d) the menopausal status at the initial diagnosis, at first recurrence and at the start of combination chemotherapy.

Table 1. Criteria for inclusion in the study

Histological confirmation of recurrent or inoperable breast cancer or radiological and/or radioisotopic evidence of metastases available for review
Objective evidence of progressive disease at the start of combination chemotherapy
Bulk of clinical disease evaluable by either direct or radiographic measurement
Performance status $\geqq 50$ and life expectancy $\geqq 2$ months
Four weeks should have elapsed from endocrine ablation, or cessation of additive hormone therapy, or discontinuation of radiotherapy

Prior to the start of treatment, all patients were accurately screened through complete physical examination; X-ray studies of chest, skull, total spine, pelvis and upper third of femora; liver scan and, whenever indicated, bone scan; complete blood count and other biochemical studies.

Patient population

The main characteristics of patient population are reported in Table 2. Only a fraction (183/318) of patients received their first treatment in our Institute. One hundred and eighty-six women (58%) were classified as operable breast cancer at first diagnosis and they all underwent radical mastectomy. Fifty-three per cent also received postoperative radiation therapy, while 7% were subjected to adjuvant castration in other hospitals. At the diagnosis of recurrent disease, only 31% (58 of 186) received combination chemotherapy as treatment of first choice.

Table 2. Characteristics of 318 patients

	No.	%
Stage at initial diagnosis		
Operable (T_1–T_2–T_{3a})	186	58
Locally advanced (T_{3b}–T_4)	73	24
Disseminated (M+)	59	18
Menopausal status at start of chemotherapy		
Premenopause	62	20
Postmenopause within 2 yr	93	29
Postmenopause 2–10 yr	87	27
Postmenopause > 10 yr	76	24
Median age (yr)	52.5	(25–74)

A total of 42% (132 of 318) had no disease-free interval, either because the patients had locally advanced T_{3b}–T_4 disease, and never experienced a period of tumor regression after radiotherapy or other types of treatment, or because physical and/or radiological examinations revealed the presence of distant metastases (M+) at the time of first diagnosis. Forty-seven per cent of these women (62 of 132) received combination chemotherapy as a first treatment. Consequently, a total of 62% (198 of 318 patients) had received prior radiotherapy (postoperative or palliative), a single agent of chemotherapy and/or different forms of hormonal manipulation at the diagnosis of recurrent or advanced breast cancer. In many women combination chemotherapy was administered when they became refractory to almost all endocrine treatments.

At the start of the chemotherapy, 80% of the patients were postmenopausal, while the other patients were considered to be premenopausal as less than one year had elapsed from their last menstrual period. Moreover, 77% (48 of 62) of premenopausal patients were still having regular menses.

Table 3 shows the various patterns of disease extension prior to the start of chemotherapy. Soft tissue involvement alone was present in 39%, while osseous and visceral lesions were 24 and 37%, respectively.

The types of combinations studied in our Institute as well as their overall results are summarized in Table 4. No important differences were detected. The lower response and survival rates reported for CMFV combination compared to the other regimens are probably due to an extensive and prolonged

Table 3. Patterns of disease extension at the start of combination chemotherapy

Extension	No.	%	
Local-regional only	87	27	39%
Soft tissue ± local regional	39	12	
Bone only	14	4	24%
Bone + soft tissue	62	20	
Viscera only	31	10	37%
Viscera + soft tissue	45	14	
Viscera + bone	22	7	
Viscera + bone + soft tissue	18	6	

Table 4. Type of combinations and their response

Combination	No. patients	% Response (CR + PR)	Median* duration of response (mos)	Median overall survival (mos)
CMFV	59	49	7.5	12
AVP	20	55	10	18
AV	65	55	10.5	22
CMF	60	55	11	20
CMF–AV†	114	61	12	23

C: cyclophosphamide, M: methotrexate, F: fluorouracil, V: vincristine. A: adriamycin, P: prednisone.
*From start of chemotherapy.
†Sequential combinations.

prior treatment before the beginning of chemotherapy [3]. It is important to point out that within the various treatment groups there was no significant difference among the main clinical characteristics (disease presentation, menopausal status) before starting chemotherapy. However, in the group given sequential chemotherapy (CMF-AV) a higher percentage of premenopausal women were entered [4].

Follow-up and criteria of response

Patients were accurately examined during the treatment with combination chemotherapy. Besides complete blood counts before drug injection, physical examination was performed once a month. The planned routine follow-up studies included chest X-ray and blood chemistry every three months, skeletal survey, liver scan and, whenever possible, bone scan every six months. However, when it was felt justified either to assess tumor regression, or in the presence of suspicious progression or relapse, all physical and radiological studies were simultaneously repeated. All patients were treated in the out-patient clinic of the Institute.

The criteria for assessment of response are those already reported in our previous publications [3–6]. Briefly, they are defined as follows:
Complete remission (CR): disappearance of all known sites of disease, with recalcification of lytic metastases, for at least one month;
Partial remission (PR): at least a 50% decrease of all measurable lesions with partial recalcification of osteolytic metastases, associated to improvement in evaluable but non-measurable lesions, for at least one month;
No response: lesions unchanged, or decreased to less than 50%, or increased to less than 25% in the size of measurable lesions. Also patients in whom non-measurable, but evaluable lesions representing the bulk of disease, did not respond were categorized as no response.
Progression: greater than 25% increase in the size of any measurable lesion and/or appearance of new lesions.

Statistical analysis

Statistical analysis was carried out on a total proportion of responses. To determine the level of significance the chi-square test was calculated in each subgroup of patients. The patient survival from the beginning of chemotherapy was analyzed according to standard life table methods. The probability of differences among subgroups was calculated by the use of the Mantel method of the Wilcoxon test [7].

RESULTS

Table 5 indicates the overall results obtained in 318 patients regardless of the regimen administered. As already universally observed, responders (56.3%) showed a longer survival compared to failures, the difference being highly statistically significant ($P < 0.00001$).

Table 5. *Type of response in* 318 *patients*

CR + PR ≥ 50%	179/318 (56.3%)
Median duration of response from start of chemotherapy	10.5 months
Median overall survival	19 months
Median survival in responders	24.5* months
Median survival in non-responders	11.5* months

*$P < 0.00001$.

Response related to disease-free interval

In this series (Table 6), the response rate (CR plus PR) was inversely proportional to the disease-free interval, highest in those initially showing disseminated disease (69.5%) and lowest in those with free interval > 5 yr (40%). Following the suggestion of Hayward *et al.* [8], we subdivided patients with no disease-free interval into two subjects, those with distant metastases and those presenting with locally advanced (T_{3b}–T_4) breast cancer. However, from our data, these two subgroups did not seem to carry a different prognosis since the median survival for responders was similar (27 vs 26 months).

The lowest survival was observed in the subgroup of patients who relapsed within 2 yr from radical mastectomy. In fact, in spite of the high response rate (53.8%) a rapidly further dissemination occurred, and the median survival was only 19 months, a duration which is very short for responders. Furthermore, only 15% of these patients were still alive at 3 yr in comparison to 30–40% of responders in other subgroups.

Response related to menopausal status

The data reported in Table 7 show that early postmenopausal patients (i.e., those in whom less than 2 yr had elapsed from their last menstrual period) carry a very poor prognosis. Only 46.2% responded to the treatment and the median survival for responders did not exceed 18 months. A similar short median survival was observed in responders who were more than 10 yr postmenopausal despite their high remission rate (57.9%).

Response related to disease extent

No significant difference in terms of response and survival rates could be detected among the three categories of dominant disease (Table 8). However, in patients with concomitant visceral, osseous and soft tissue involvement, both response (38.9%) and median survival (15 months) were inferior when compared with the other subgroups. Eight per cent were still alive at 2 yr, but none are expected to be alive at 3 yr. Although this is a small group of patients we have no evidence that the presence or absence of the liver involvement was affecting either the response or the survival.

Response related to prior systemic treatment

Of 198 patients who were previously trea-

Table 6. *Response and survival related to free interval*

		No.	% CR + PR	Median survival (months) Responders	Non-responders
No interval	Distant mets	59	69.5	27	9
	T_{3b}–T_4	73	57.5	26	14
< 2 yr		104	53.8	19	10
≥ 2 yr		82	48.8	25	14

Survival in responders: no interval vs < 2 yr $P < 0.01$; ≥ 2 yr vs < 2 yr $P = 0.02$.

Table 7. Response and survival related to menopausal status

	No.	% CR + PR	Median survival (months) Responders	Non-responders
Premenopause	62	64.5	26	16
Postmenopause within 2 yr	93	46.2	18	6
Postmenopause 2–10 yr	87	59.8	27	18
Postmenopause > 10 yr	76	57.9	19	10

CR + PR: premenopause vs post <2 yr $P=0.04$.
Survival in responders: premenopause vs post <2 yr $P=0.08$; premenopause vs post > 10 yr $P=0.08$.

Table 8. Response and survival related to disease extension

	No.	% CR + PR	Median survival (months) Responders	Non-responders
Soft tissue	126	61.1	25	15
Bone ± soft tissue	76	60.5	23	15
Viscera (alone or associate to either bone or soft tissue)	98	50.0	23	10
Viscera + bone + soft tissue	18	38.9	15	10

CR + PR: soft tissue vs viscera + bone + soft tissue, $P=0.07$.
Survival in responders: soft tissue vs viscera + bone + soft tissue, $P=0.08$.

ted before starting combination chemotherapy, 144 (73%) had received hormonal manipulations with a total CR plus PR of 25%.

Table 9 shows that prior endocrine therapy unfavorably affected the rate of response when compared with no prior therapy. However, there was no statistical difference when the median survival of responders was considered. There was not a direct correlation between response to prior endocrine therapy and response to combination chemotherapy.

DISCUSSION

The results of our retrospective study on patients treated with regimens producing similar rates of response indicate that disease-free interval < 2 yr, early postmenopausal status, concomitant lesions in soft tissue, bone and viscera as well as prior endocrine therapy are all important prognostic prechemotherapeutic variables.

Other authors have reported that short disease-free interval was associated with unfavorable prognosis [9, 10]. In our series, disease-free interval < 2 yr from radical mastectomy unfavorably affected the median survival rate after effective combination chemotherapy. On the contrary, patients with no disease-free interval (i.e., those with locally advanced or disseminated disease at diagnosis)

*Table 9. Response and survival related to prior treatment**

		No.	% CR + PR†	Median survival Responders	Non-responders
No prior treatment		120	73.3	27	18
Prior endocrine treatment	Responders	37	43.2	24	19
	Non-responders	107	45.8	21	10

*54 patients who received either prior RT or single agent chemotherapy were excluded.
†No prior treatment vs prior endocrine treatment: $P<0.0001$.

appeared to do better than patients with short disease-free interval. The same observation was also recently made by George and Hoogstraten [10]. Therefore, as far as this prechemotherapeutic variable is concerned, study patients should be stratified into three groups: no free interval, < and ≧2 yr.

Almost no data are available on menopausal status vs response to combination chemotherapy in advanced breast cancer. In his recent review, P. P. Carbone [11] mentioned that remission rate was not influenced by menopause while George and Hoogstraten [10] noticed that older patients seemed to show higher response rates only when treated with adriamycin. However, in our series a detailed analysis on patients treated with adriamycin plus vincristine (AV) failed to confirm this observation as both response and survival rates did not favor postmenopausal women. In our series of 93 women who were postmenopausal within 2 yr at the start of chemotherapy, both response and survival were lower in comparison with other subgroups except for the survival in postmenopausal women > 10 yr. While it is conceivable that the lower dose schedule, applied to women older than 65 yr [5, 6], could be responsible for the shorter duration of response and, consequently, of the median survival, in early postmenopausal patients no clinical findings could be found to explain the marked reduced response and survival rates. It could be possible that unknown biological factors, such as tumor-host interactions, were involved in this particular subgroup. Therefore, from our data, prechemotherapy stratification should include premenopause, postmenopause within 2 yr and postmenopause ≧2 yr.

Contrary to what has been universally reported in the past with endocrine therapy, and recently with combination chemotherapy by Brunner *et al.* [12], our series failed to indicate that after multiple drug regimens response and survival were related to the dominant sites of the lesions. Our findings are in agreement with those of Ahmann *et al.* [13]. It is important to point out that in women with bone plus soft tissue extension we have based the response rate on objective tumor regression in soft tissue lesions only when associated with concomitant evidence of initial healing in bone lesions. It is also worth noting that the presence of liver metastases did not influence *per se* both response and survival rates as previously observed by other investigators [10, 14]. On the contrary, as also reported by Brunner *et al.* [9], the prognosis was adversely affected by the presence of high total tumor cell burden as represented by the concomitant clinical involvement of visceral, osseous and soft tissue lesions.

Finally, prior endocrine therapy was associated with poor response to combination chemotherapy. The fact that there was no difference between responders and non-responders to hormonal manipulations once they were subjected to combination chemotherapy, confirms the absence of cross resistance between the two modalities. This would also indicate that either a slow growing disease or a more advanced disease (higher total tumor cell burden) or a combination of both was responsible for the decreased response to chemotherapy. For this reason, prior endocrine therapy *per se* should probably not be considered a pre-chemotherapeutic variable also because prior endocrine therapy did not affect survival after chemotherapy.

In conclusion, some of our findings run counter to most traditional concepts on prognostic variables for advanced breast cancer as developed in patients treated with endocrine manipulations. In particular, our results would indicate that the classical concept of "dominant disease" needs to be revised when the patients are candidates for a study with combination chemotherapy. In future studies, new parameters, such as estrogen receptor determination, could be useful to predict the response not only to endocrine therapy [15] but also to combination chemotherapy [16]. However, they still lack specific predictivity for identifying potential responders with the high degree of reliability that would allow most patients to avoid unrewarding major endocrine therapy. At present, the major contribution of estrogen receptor assay is to spare the receptor negative patients the complications and lack of benefit of endocrine treatment. Furthermore, there is also a need for a more uniform method of reporting the results of systemic therapy to facilitate the comparison among published reports. A full re-evaluation of traditional prognostic parameters, even in women given endocrine therapy, is advisable once the assessment of response has been clearly defined. Survival and response distribution analysis, as well as categorization of results by pre-therapeutic variables, would be helpful for interstudy comparison.

Our study re-emphasizes once more that, in advanced breast cancer, different polydrug regimens yield approximately similar thera-

peutic results. Available drugs are unable to achieve a sustained control of responsive patients, probably because of the very high tumor cell burden at the start of treatment. This is the main reason why trials on surgical adjuvant chemotherapy are so important since, in an adjuvant situation, the tumor cell burden is still limited and, therefore, susceptible of being effectively influenced by current drug regimens [17].

REFERENCES

1. M. Rosencweig and J. L. Heuson, Breast cancer: Prognostic factors and clinical evaluation. In *Cancer Therapy: Prognostic Factors and Criteria of Response.* (Edited by M. J. Staquet) p. 139. Raven Press, New York (1975).
2. International Union Against Cancer, Committee on TNM Classification. *TNM Classification of Malignant Tumors*, 2nd Edn. Geneva, International Union against Cancer (1974).
3. M. de Lena, G. M. de Palo, G. Bonadonna, G. Beretta and E. Bajetta, Treatment of metastatic breast cancer with cyclophosphamide, methotrexate, vincristine and fluorouracil. *Tumori* **59,** 11 (1973).
4. C. Brambilla, P. Valagussa and G. Bonadonna, Sequential combination chemotherapy in advanced breast cancer. *Cancer Chemother. Pharmacol.* **1,** 35 (1978).
5. M. de Lena, C. Brambilla, A. Morabito and G. Bonadonna, Adriamycin plus vincristine compared to and combined with cyclophosphamide, methotrexate and 5-fluorouracil for advanced breast cancer. *Cancer (Philad.)* **35,** 1108 (1975).
6. C. Brambilla, M. de Lena, A. Rossi, P. Valagussa and G. Bonadonna, Response and survival in advanced breast cancer after two non-cross resistant combinations. *Brit. med. J.* **1,** 801 (1976).
7. N. Mantel, Ranking procedure for arbitrarily restricted observation. *Biometrics* **23,** 65 (1967).
8. J. L. Hayward, P. P. Carbone, J. C. Heuson, S. Kumaoka, A. Segaloff and R. D. Rubens, Assessment of response to therapy in advanced breast cancer. (A project of the programme on clinical oncology of the International Union against Cancer, Geneva, Switzerland.) *Europ. J. Cancer* **13,** 89 (1977).
9. K. W. Brunner, Present status of combination chemotherapy in advanced breast cancer. *Antibiot. et Chemother. (Basel)* **24,** 173 (1978).
10. S. L. George and B. Hoogstraten, Prognostic factors in the initial response to therapy by patients with advanced breast cancer. *J. nat. Cancer Inst.* **60,** 731 (1978).
11. P. P. Carbone, Tumor biology and clinical trials: the Richard and Hinda Rosenthal Foundation Award Lecture. *Cancer Res.* **37,** 4239 (1977).
12. K. W. Brunner, R. W. Sonntag, P. Alberto, H. J. Senn, G. Martz, P. Obrecht and P. Maurice, Combined chemo- and hormonal therapy in advanced breast cancer. *Cancer (Philad.)* **39,** 2923 (1977).
13. D. L. Ahmann, H. F. Bisel, R. G. Hahn, R. T. Eagan, J. H. Edmonson, J. L. Steinfeld, D. C. Tormey and W. F. Taylor, An analysis of a multiple-drug program in the treatment of patients with advanced breast cancer utilizing 5-fluorouracil, cyclophosphamide and prednisone with or without vincristine. *Cancer (Philad.)* **36,** 1925 (1975).
14. G. P. Canellos, S. J. Pocock, S. G. Taylor, III, M. E. Sears, D. J. Klaasen and P. R. Band, Combination chemotherapy for metastatic breast cancer: prospective comparison of multiple drug therapy with L-phenylalanine mustard. *Cancer (Philad.)* **38,** 1882 (1976).
15. W. L. McGuire, K. B. Horwitz, D. T. Zava, R. E. Garola and G. C. Chamness, Hormones in breast cancer: update 1978. *Metabolism* **27,** 487 (1978).
16. M. E. Lippman, J. C. Allegra, E. B. Thompson, R. Simon, A. Barlock, L. Green, K. K. Huff, H. M. T. Do, S. C. Aitken and R. Warren, The relation between estrogen receptors and response rate to cytotoxic chemotherapy in metastatic breast cancer. *New Engl. J. Med.* **298,** 1223 (1978).
17. G. Bonadonna, P. Valagussa, A. Rossi, R. Zucali, G. Tancini, E. Bajetta, C. Brambilla, M. de Lena, G. di Fronzo, A. Banfi, F. Rilke and U. Veronesi, Are surgical adjuvant trials altering the course of breast cancer? *Semin. Oncol.* (to be published).