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Special Paper

Current and Future Trends in the Multidisciplinary Approach for High-risk Breast Cancer. The Experience of the Milan Cancer Institute*

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INTRODUCTION

DURING THE last 25 years the concept of distant micrometastases in subsets of patients with conventionally operable breast cancer has been successfully tested through prospective randomised trials involving the early use of systemic chemotherapy [1, 2]. Over the years, the consistency of therapeutic findings has given medical oncology a central role in the overall treatment strategy for breast cancer and has resulted in a profound revolution in the approach, management and evaluation of breast cancer.

This paper will review the most notable long-term results achieved through novel multidisciplinary approaches by the Milan Cancer Institute. It will also briefly outline possible future developments which attempt to improve distant disease control and to redefine what is the true adjuvant treatment.

TRIALS CONFIRMING THE INITIAL HYPOTHESES

The recently published 20-year results of the first CMF (cyclophosphamide, methotrexate and 5-fluorouracil) adjuvant programme [3] confirmed the initial biological hypotheses that pioneering investigators [4–6] had formulated on the basis of experimental animal data (Table 1). In fact, clinical studies have consistently demonstrated that most women presenting with node positive breast cancer do not have a localised disease, and that early administration of adjuvant chemotherapy following surgery is able to improve significantly both relapse free and total survival rates. Furthermore, the analysis of long-term results also confirmed the prognostic importance of the received dose rate, a finding supported by recent data from a prospective randomised trial [7]. Thus, modern, effective drug programmes indicate that for both node positive and high-risk node negative tumours, treatment outcome is very similar between premenopausal and postmenopausal women, and that in patients given full dose chemotherapy, drug-induced amenorrhoea is not an important predictor of response (Table 2).

Table 1. Biological hypotheses which led to modern multidisciplinary treatment strategy for resectable breast cancer

No orderly pattern of tumour cell dissemination.
Frequent dissemination through the blood stream.
Operable breast cancer is a systemic disease.
Surgical adjuvant chemotherapy increases the long-term cure rates.
The efficacy of chemotherapy is dose dependent and related to the tumour cell burden.

The CMF lesson has been instructive from several points of view. First, the magnitude of treatment results is related to the various nodal categories, being maximal in node negative tumours and minimal in tumours with > 10 positive axillary nodes. This finding can be interpreted as an indirect sign of the societal aspects of malignant cells. In fact, laboratory investigations have demonstrated that breast cancers (as well as other solid tumours) are composed of diverse cell populations which are heterogeneous for a variety of characteristics including genetic, biochemical, immunological and biological properties [8]. The two most sinister aspects of intraneoplastic diversity are the genesis of clones with metastatic potential, and the existence of drug-resistant variants in the primary malignancy and its metastases. Since primary drug resistance has long been identified as a major reason for treatment failure, the critical problem is how many subpopulations are present in a heterogeneous tumour such as breast cancer. Considering that the multifactorial phenomenon of intraneoplastic diversity is dynamic and constantly changing with time, it is not unreasonable to hypothesise the existence of many thousands of clones, including several hundred drug-resistant variants in 1 g of solid tumour containing 1 billion cancer cells [9]. The number and fraction of drug-sensitive versus drug-resistant tumour cells fluctuate considerably

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* FECS Award lecture, given on October 30 1995 during ECCO-8 at the Palais de Congres in Paris, France. Unfortunately, Dr Gianni Bonadonna, Milan, Italy, was prevented from giving this lecture himself due to sudden illness. We were recently assured that he is recovering successfully and we wish him all the best.

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Table 2. Essential therapeutic results from the CMF adjuvant trials performed at the Milan Cancer Institute [3, 11]

Node positive tumours

First study: CMF for 12 cycles versus control (386 patients)

At 20 years

	CMF	CTR	
RFS	32%	25%	$P < 0.001$
OS	34%	23%	$P = 0.03$

Full dose CMF improved outcome (RFS 49%, OS 52%)

Drug-induced amenorrhea was not an important predictor of response

Second malignancies were not a major problem

Second study: CMF 12 versus 6 cycles (459 patients)

At 18 years

No statistically significant difference relative to treatment duration

No statistically significant difference between pre- and postmenopausal women

Node negative and ER negative tumours

CMF i.v. 12 courses versus control (90 patients)

At 12 years

	CMF	CTR	
RFS	71%	48%	$P = 0.008$
OS	80%	50%	$P = 0.03$

Treatment outcome after CMF was unrelated to tumour size, grade and proliferative activity

No difference between pre- and postmenopausal women

CTR, control group (surgery alone); RFS, relapse free survival; OS, overall survival; ER, oestrogen receptor.

Table 3. Essential therapeutic results from sequential adjuvant chemotherapy trials in node positive tumours performed at the Milan Cancer Institute [10–12]

Nodes 1 to 3

CMF i.v. 12 courses versus CMF for 8 courses → doxorubicin for 4 courses (552 patients)

At 10 years

The addition of doxorubicin after CMF failed to improve both RFS and OS over CMF alone

No difference between pre- and postmenopausal women

Nodes > 3

Doxorubicin (DOX) → CMF vs CMF/DOX (403 patients)

At 10 years

	DOX → CMF	CMF/DOX	
RFS	42%	28%	$P = 0.001$
OS	58%	44%	$P < 0.001$

After DOX → CMF no difference between pre- and postmenopausal women

Nodes ≥ 10

Non-randomised study with high-dose sequential (HDS) regimen combined with GM-CSF or G-CSF and peripheral blood progenitor cell support (67 patients)

At 5 years

Significantly superior RFS and OS compared to a similar patient subset given doxorubicin → CMF

RFS, relapse free survival; OS, overall survival.

within micrometastatic colonies of the same size, and therefore even when the tumour population is small clinicians must face the possibility that a single patient with breast cancer may indeed have many diseases. Therefore, extensive axillary involvement (for example > 3 positive nodes) should probably be utilised as an indirect marker of frequent drug resistance among micrometastatic deposits, thus requiring chemotherapy programmes more complex than CMF. The data concerning the lack of significant difference between 12 and six cycles of adjuvant CMF (Table 2) should also be interpreted as an indirect sign of resistant cell lines.

SEQUENTIAL NON-CROSS-RESISTANT AGENTS

In the attempt to circumvent, in part, the phenomenon of primary drug resistance, new adjuvant trials were designed in the early 1980s at the Milan Cancer Institute testing sequential non-cross-resistant agents. In patients with resectable breast cancer and more than three positive axillary lymph nodes, sequential versus alternating doxorubicin (DOX) and CMF were randomly compared. The recently published 10-year results [10] confirmed that treatment outcome was significantly superior for patients who received the sequential regimen compared with those given the alternating chemotherapy (Table 3). With the only variation being drug sequence, the median duration of relapse free survival was almost doubled after sequential DOX → CMF (86 months) compared with alternating CMF/DOX (47 months). Of particular importance, total survival difference between the two treatment groups also remained statistically significant, and at 10 years median survival of women given sequential chemotherapy has not been reached. In contrast, the alternating schedule produced inferior results that were similar to the schedule that used CMF alone. This achievement in a poor-risk subset could probably be explained by the use of full dose size, dose intensity and the sequence of two effective non-cross-resistant drug regimens. In the sequential arm, the intensity of doxorubicin administration was increased, and by itself could account for the superiority of the cross-over treatment. In the patient subset presenting with one to three positive nodes [11], the administration of four cycles of doxorubicin after CMF failed to yield superior results compared to the delivery of CMF alone (Table 3). This observation confirmed that the type of drug sequence is important, and further studies on this topic could provide more biological insights into the design of optimal combination regimens.

Another important study with sequential non-cross-resistant chemotherapy involved the administration of high drug doses. The purpose of this prospective non-randomised trial was to assess the efficacy, toxicity and applicability of a novel high-dose sequential (HDS) regimen combined with haematopoietic growth factor (GM-CSF, G-CSF) and autografting of cryopreserved peripheral blood progenitor cell support as adjuvant initial treatment for patients with ≥ 10 positive axillary nodes. The details of this study, involving 67 women, were recently reported by Gianni and associates [12].

The HDS regimen consisted in the administration of three non-cross-resistant agents (cyclophosphamide, methotrexate and melphalan) given as closely spaced as compatible with haematological and non-haematological toxicity. After a median follow-up observation of 48.5 months and a lead follow-up of 78 months, the actuarial relapse free survival was 57% and total survival 70%, respectively. Table 4 compares the data of HDS with those of a historical control group of 58 consecutive patients given doxorubicin followed by CMF

Table 4. Sequential adjuvant chemotherapy in patients with ≥ 10 positive nodes. Five-year results (%) in two successive studies at the Milan Cancer Institute

	RFS	OS
Total series		
HDS	57	70
DOX → CMF	41	60
Nodes 10–15		
HDS	65	77
DOX → CMF	42	61

HDS, high-dose sequential regimen; RFS, relapse free survival; OS, overall survival.

[12]. Such a comparison shows a significantly superior rate of freedom from relapse for the HDS-treated group while the rates of total survival are not significantly different. Both comparative findings were significantly in favour of HDS when patients were compared in the presence of a more homogeneous number of positive nodes. Overall, HDS chemotherapy was of a short duration (median 70 days), subjectively well tolerated, required limited transfusional support, and patient care, and an average of 32 days of hospital stay. HDS sequential treatment is now being randomly compared with epidoxorubicin followed by CMF in all patients presenting with greater than three involved lymph nodes.

WINDS OF CHANGE: PRIMARY CHEMOTHERAPY

Overall, controlled trials with systemic adjuvant treatments conceived and performed from the early 1970s have improved both relapse free and total survival rates at 10 years as validated by the International Overview [13]. The long-term results of such trials also contributed to modification of the traditional concepts of "radical" surgery, for treatment outcome was not related to the extent of operation but rather to the type of drugs utilised and their received dose intensity. Hence, in women whose tumour characteristics are at high (≥ 20%) risk of harbouring distant micrometastases (Table 5), the therapeutic challenge is indeed outside the mammary gland and its regional lymph nodes.

The possibility that in high risk subsets surgery may not represent the correct form of primary therapy stimulated a few medical oncologists to initiate treatment with drugs rather than with a local–regional modality. The first attempts with primary (neoadjuvant, pre-operative, pre-irradiation) chemotherapy originated from the need to achieve, in locally advanced breast cancer, prompt tumour response using only a few chemotherapy cycles to facilitate the delivery of either mastectomy or radiotherapy or both modalities [14, 15]. Following the initial experience yielding promising results, the concept of primary chemotherapy has captured the imagination of an ever expanding population of clinical oncologists to spare mutilating surgery in women otherwise candidate to mastectomy. In more recent years, and due to the results achieved with new cytotoxic drugs, a few proper trials were initiated to determine whether, in high-risk women, locoregional rather than systemic therapy should be considered the true adjuvant treatment [15, 16].

Table 5. Main characteristics of primary tumour which are associated with ≥ 20% risk of distant micrometastases

T ≥ 1 cm and negative hormone receptors
T > 2 cm and positive hormone receptors
Positive axillary node involvement
Poor nuclear grade
High proliferative activity
Increased neovascularisation
p53 overexpression

The use of chemotherapy before surgery is supported by important laboratory observations showing that, in many animal models, the presence of a primary malignancy inhibits metastatic cell proliferation while removal of the primary neoplasm accelerates metastatic cell proliferation. Non-curative surgical cytoreduction shifts the cell kinetics of surviving cancer cells from a plateau to a steeper portion of the growth curve, causing a measurable increase in the proliferation rate and probably also a decrease in the lifespan of the animals. As shown by Fisher and colleagues [17,18], the removal of the primary tumour in C3H mammary adenocarcinoma is followed within 24 h by an increase in the labelling index of distant metastases, while the administration of cyclophosphamide showed its greatest cytotoxic effect when the drug was administered pre-operatively. More recent experiments have taken into consideration the role of angiogenesis [19, 20]. In Lewis lung carcinoma and T241 fibrosarcoma, Holmgren and coworkers [21] observed that the infiltration of endothelial cells in growing lung metastases was detected as early as 5 days after resection of primary tumour, and the growth of metastases correlated temporarily with the onset of neovascularisation. The authors concluded that the primary tumour secretes a potent endogenous angiogenesis inhibitor, angiostatin, which acts by preventing neovascularisation of metastatic deposits. Thus, it is quite possible that human breast cancers also produce a specific angiogenesis inhibitor which, like an endocrine hormone, inhibits the growth of micrometastases. In women with node positive or node negative breast cancer, multivariate analysis has shown that intratumoral microvessel density represents the strongest independent predictor of treatment outcome [22, 23].

Two recent review articles [14, 15] have summarised the most pertinent data achieved by several research groups with various primary drug specimens. Briefly, despite the heterogeneity in patient selection and evaluation, as well as the type of drugs and doses utilised, breast conservation rates ranged from 62 to 87%. The data from the two large studies initiated at the Milan Cancer Institute [14, 24] clearly indicated that various drug regimens, given at full dose, could induce prompt tumour shrinkage which allowed limited breast surgery such as quadrantectomy plus complete axillary dissection (Table 6). In addition, and more importantly, prognosis was related to the degree of tumour response for all but 1 of the 11 patients achieving pathological complete remission, remained alive and disease free at the 6-year analysis [15]. The lesson is clear: primary chemotherapy should include a full dose regimen of the most effective drugs in order to facilitate the achievement of pathological complete remission which appears to represent a marker of treatment outcome.

NEWER CYTOTOXIC DRUGS

In recent years, new cytotoxic drugs, namely vinorelbine and taxanes (paclitaxel and docetaxel) have proved to be very

Table 6. Main results with primary chemotherapy in two successive studies at the Milan Cancer Institute

Initial tumour diameter	No. subjected to surgery	Tumour diameter at surgery: 0.1–2 cm (%)	Complete remission: Gross (%)	Complete remission: Micro (%)	Conservative surgery (%)
≤ 4.0 cm	221	60	6	3	95
4.1–5.0 cm	136	43	9	3	86
> 5.0 cm	67	24	15	1.5	66
Total	424	49	8	3	87

effective in overt metastatic breast cancer, even when patients have been previously treated with anthracyclines [25–27].

Paclitaxel has been tested by numerous institutions worldwide. Its currently recommended schedule consists of a 3-h infusion repeated every 3 weeks [28, 29] with doses ranging from 175 to 250 mg/m^2. As a single agent, paclitaxel induces response rates in approximately 40% of patients refractory to anthracyclines [29]. The most impressive results have been those achieved when paclitaxel has been combined with anthracyclines in previously untreated patients, as exemplified by the study carried out at the Milan Cancer Institute (Table 7). Reversible cardiac effects were recorded in some patients receiving a cumulative dose of doxorubicin equal to 480 mg/m^2 [30]. Docetaxel administered at the dose of 100 mg/m^2 appears equally as effective as paclitaxel although a comparative randomised study has not yet been carried out. Such a study will be mandatory to assess objectively the cost–benefit ratio of docetaxel, a drug often associated with skin toxicity and fluid retention [27]. Under similar disease situations, vinorelbine appears as effective as both taxanes, but its minimal non-haematologic toxicity probably makes this drug easier to administer (Table 8). The response rate of vinorelbine plus anthracyclines in chemotherapy-naïve breast cancer remains largely unknown although in a few limited case series, tumour regressions have been reported in over 70% of patients [25].

How can we exploit the aforementioned data to improve the control of breast cancer? Collectively, all clinical studies performed during the past two decades have indicated that new drugs, schedules, doses and strategies improved treatment response and outcome in most breast cancer subsets. As a consequence of better tools and properly conducted trials, medical treatment (in particular full dose chemotherapy) has gained a more central role within the primary treatment of this common malignancy. Safe dose schedules including taxanes and/or vinorelbine should be incorporated into novel regimens aimed at improving the pathological complete remission rate. In fact, as already mentioned, there is preliminary evidence from the neoadjuvant Milan trials that the degree of primary tumour response could be considered as a useful (and economic) marker for predicting distant relapse free and total survival [14, 15].

Table 7. Results of paclitaxel alone and in combination with doxorubicin in disseminated breast cancer. Data from the Milan Cancer Institute [29, 30]

Patients refractory to anthracycline		
Response rate		38%
In combination with doxorubicin for untreated breast cancer (number of patients)		
Total with response	30/32	94%
Complete	13	42%
Partial	17	53%
Response rate related to disease site		
Soft tissue		96%
Bone		100%
Viscera		89%

Table 8. Vinorelbine in disseminated breast cancer largely treated with prior CMF and anthracyclines. Data from the Milan Cancer Institute [31]

	No. of patients	%
Total with response	25/53	47
Complete	4	7
Partial	21	40
Response related to dominant disease site		
Soft tissue	7/13	54
Viscera	13/31	42
Bone	5/9	56

FUTURE DEVELOPMENTS

During the past 25 years, the management of breast cancer has been dramatically influenced by new ideas and discoveries corroborated by sound long-term results. In particular, the results from randomised trials involving breast-conserving surgery and systemic adjuvant therapy have formed the new paradigm governing current clinical practice [1, 2]. The findings of such trials also paved the road to subsequent clinical and laboratory studies including the first attempts to determine the usefulness of primary chemotherapy. Having confirmed on clinical grounds that, in many patient subsets, operable breast cancer is predominantly a microdisseminated disease, it is now the proper time to conceive a more radical departure from the old dogma, i.e. resectable tumours must always be excised as first therapeutic approach.

Many years ago, Bernie Fisher stated that it was "becoming increasingly meaningless for surgeons to discuss the surgical management of breast cancer without consideration of how other therapeutic modalities might replace (or influence) their operative approach" [16]. The diminished role of surgery in the primary treatment of breast cancer, as well as the strategic

role of drug therapy in high risk subsets, should now open the possibility of generating new innovative trials aimed at increasing the cell kill of distant micrometastases. Such an opportunity may now be provided by potentially more effective pre-operative drug regimens. This new strategy should be able to transform the role of surgery so an operation would aid systemic treatment in achieving curability. An example of a randomised trial required to assess the true adjuvant treatment is outlined in Figure 1. In particular, the aims of the new Milan trial in tumours > 2 cm upon mammography are: (a) to determine whether primary chemotherapy with two non-cross-resistant regimens (anthracycline plus paclitaxel followed by CMF) can more effectively improve distant relapse free and total survival compared to the same sequential drug regimen given in a surgical adjuvant setting; (b) to compare at the completion of either entire treatment programme old and new prognostic variables. The study will be carried out in subsets with ≥ 30% risk of having distant micrometastatic foci.

Will primary chemotherapy eventually replace breast surgery? In my opinion, well conceived and executed drug regimens should be able to eliminate the need for mastectomy in almost all women. Some of the patients presenting with bulky disease (> 7 cm in largest diameter)—a biological situation often associated with a high proportion of drug-resistant cells—may still require removal of the entire breast despite prompt tumour shrinkage. However, this will be the exception, not the rule. In women achieving complete or almost complete tumour disappearance at mammography and/or needle aspiration, appropriate controlled studies should define whether breast surgery could be replaced by breast irradiation. In the remaining patients showing good partial response at the completion of chemotherapy, breast conservative surgery plus axillary node dissection or sampling will probably remain a necessary procedure depending on the size of the residual lump.

In order to increase the magnitude of primary tumour shrinkage, high dose sequential chemotherapy with haematopoietic support should also be tested in future randomised trials compared with the best available conventional drug regimen(s). Modern delivery of high-dose regimens not only confirmed that the pharmacological principle of dose response effect is also valid in the chemosensitive malignancies, but also proved to be safe and relatively non-toxic in an adjuvant situation [12]. Because of its shorter duration compared to conventional drug combinations, high-dose chemotherapy also deserves to be investigated as primary chemotherapy in selected patients. Last but not least, angiogenesis inhibitors should become available for testing in an adjuvant situation in conjunction with chemoendocrine treatments [19].

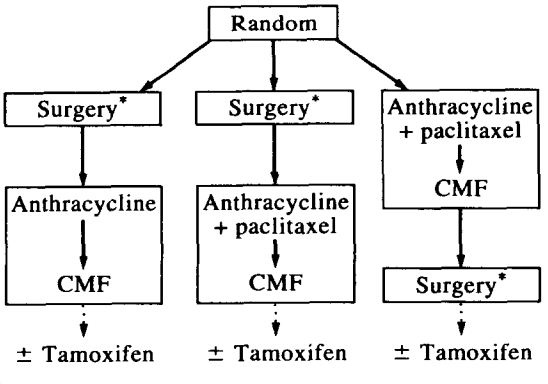

Figure 1. Example of a cooperative trial in breast cancer > 2 cm. The study will be started in 1996.

In conclusion, at the end of this century, clinical oncologists are faced with the opportunity of abandoning outmoded paradigms which governed breast cancer treatment since the time of William Halsted. Biological hypotheses have stimulated clinical action so facts could substitute for opinions due to successive well conducted randomised trials, one of the most important innovations of our time. Younger generations of researchers are not only expected to build upon current achievements but also begin to conceive an entirely different scenario in order to make obsolete, in future decades, contemporary beliefs as well as our toxic treatments.

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