Evolving Concepts in the Systemic Adjuvant Treatment of Breast Cancer

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At the turn of this century, breast cancer ranks as the single most common female malignancy in many geographical areas of the world. Its growing incidence frightens women, puzzles scientists, challenges doctors, and keeps the media busy. Technological advances, namely early detection by mammography, a variety of breast-conserving procedures, and systemic adjuvant treatments, created survival probabilities and therapeutic implications. However, for resectable breast cancer the controversies among academic physician scientists, as publicly displayed in countless meetings, professional journals, and nonmedical articles, have generated little concrete guidance that has somewhat blurred the true clinical progress achieved in about two decades of trials and errors. Doctors and patients have become obsessed with treatment options; often they appear unable to decide.

This paper will review the evolution of scientific concepts underlying major clinical trials undertaken since the early 1970s with systemic adjuvant and neoadjuvant treatments for resectable breast cancer. To protect the readers from the deluge of reports that have appeared in the medical literature on the subject in question, this review will purposely avoid dissecting individual studies. Rather, on the basis of important treatment findings, it will attempt to provide a guide as how the strategic approach has been progressively changing in the effort to improve the control of high risk breast cancer.

Biological Hypotheses and Clinical Strategy

The golden age of adjuvant chemotherapy began in the early 1970s. At that time, a few clinical and laboratory findings helped to formulate new treatment strategies for several malignancies, in particular breast cancer (Table 1). First of all, the evaluation of two surgical trials (1, 2) challenged the principles of Halstedian hypothesis and lent clinical support to pioneering laboratory investigations (3) on the mode of spread of breast cancer. The high recurrence rate, especially during the first 3 years from Halsted, and enlarged radical mastectomies could have only one reasonable explanation, i.e. the presence of distant micrometastases at the time of surgery. The clinical challenge of the anatomic and mechanistic dogma opened the pathway to biological hypotheses and paved the road to both conservative surgery and systemic adjuvant treatment. Another important information was derived from the seminal studies carried out in experimental animal systems (4, 5). In mice bearing mammary tumors, surgery followed by chemotherapy yielded survival results superior to either modality alone. The above mentioned studies also stressed the importance of drug dose and tumor cell burden and suggested that micrometastatic foci could be more vulnerable to the effects of cell cycle-specific agents (6). A third information, which emerged from laboratory and clinical investigations, indicated that in some malignancies, namely acute leukemia, Hodgkin’s disease, and a variety of pediatric tumors, multiple drug regimens had the potential for cure (7, 8).

The early biological hypothesis concerning micrometastatic disease and potential benefit from adjuvant chemotherapy was first tested through randomized clinical trials by the NSABP (9) and the Milan Cancer Institute (10). The first NSABP study utilized single agent chemotherapy (L-phenylalanine mustard or melphalan) while the Milan trial elected to use a multiple drug regimen known as CMF. Eventually, the multidisciplinary strategy with combination chemotherapy prevailed and became the standard approach for given patient subsets (11). Many clinicians were perplexed before the early results of the new treatment strategy (9, 10), and only a few were gifted with intuition to foresee that early findings could largely predict for long-term results (12). Fortunately, in spite of numerous difficulties to cross medical compartments, many research physicians accepted the message of the multidisciplinary approach and began to set up further prospective trials.

Chemotherapy Results in Node-positive Tumors

The comparative data of the first CMF trial are now available for the 15-year analysis. The long-term results of the entire case series (total, 386 patients) confirmed once more that the scientific principles underlying clinical strategy were correct. In most patients with histologically positive axillary lymph nodes resectable breast cancer should be considered a systemic disease the micrometastatic foci of which can benefit from an intensive adjuvant systemic treatment. Besides the therapeutic advantage, trial results provided evidence or confirmation of important biological and pharmacological concepts, namely prognostic importance of tumor cell burden, dose-response effect, and clinical drug resistance.

Fig. 1A shows that the maximum recurrence rate occurred during the first 3 years from radical mastectomy; from this time on, the difference between control and CMF remained about the same for the subsequent 12 years. This observation indicated that the early findings could predict with sufficient accuracy for the late outcome and suggested that micrometastases included very aggressive cell lines mostly resistant to cytotoxic chemotherapy. Total survival difference (Fig. 1B) was progressively increasing after the seventh year from starting adjuvant therapy. As detailed in previous publications (11, 13, 14), the results of the CMF program confirmed the importance of nodal extent, for there was a consistent inverse relationship between number of involved lymph nodes and treatment outcome. The 5- and 10-year analysis provided the opportunity to review the effect of drug dose in a clinical adjuvant setting. In the first CMF program, the significant achievements in premenopausal women (Fig. 2) were not duplicated in postmenopausal patients. In this latter subset, as a consequence of trial design or protocol deviations, chemotherapy included initial low doses and was
Table 1  Clinical observations, laboratory findings, and biological hypotheses influencing the beginning of modern adjuvant chemotherapy for high risk operable breast cancer

By the time cancer becomes clinically detectable, is advanced (near 30 doublings), and has had ample opportunity to establish distant micrometastases.

Frequency of metastatic disease is directly related to tumor mass, and surgical cure rates drop as tumor volume at surgery increases.

Tumor growth fraction is inversely related to population size.

Effective drug kill follows first order reaction kinetics.

Combination of drugs is superior to single agents and can eradicate 10–100 times as many cells.

In transplantable tumors surgical adjuvant chemotherapy increases the long-term cure rates.

The optimal kinetic conditions to achieve cure exist when microscopic foci of disease are present after curative surgery and/or radiotherapy.

often arbitrarily reduced during most cycles (15). This important pharmacological aspect will be discussed later.

The results of the second CMF adjuvant program (12 versus 6 cycles in a series of 459 node-positive patients) leave room to speculate about drug resistance at clinical level. At 14 years, both relapse-free (Fig. 3) and total survival rates between treatment groups remain nonsignificant. Most probably, full or near full doses of chemotherapy, as delivered in this trial, are sufficient to kill most (at times all) drug-sensitive tumor cells while early and late relapses are due to the overgrowth of primary resistant neoplastic cells. Comparable findings with the same theoretical and practical considerations were subsequently reported by Henderson et al. (16) and Fisher et al. (17) utilizing Adriamycin-containing regimens.

The CMF adjuvant results were largely confirmed worldwide (18) and this triple drug regimen, delivered for six monthly cycles, became the standard adjuvant regimen in clinical practice.

Tamoxifen Trials

The concept that at least a fraction of breast tumors is "hormone dependent" and therefore responsive to various endocrine manipulations is an old one, supported by innumerable laboratory and clinical observations. The discovery of hormone receptors in the mid-1970s provided the rationale for a more selective application of endocrine treatment. In advanced dis-

Fig. 1. First CMF program: 15-year results. A, comparative relapse-free survival; B, comparative total survival.

Fig. 2. First CMF program: 15-year results in premenopausal women. A, comparative relapse-free survival; B, comparative total survival.
Ease endocrine ablative or additive therapies give a response rate of 30% in unselected patients, around 50% in ER-positive, and as high 80% when both ER and progesterone receptor are positive. Only 5–10% of receptor-negative tumors will respond to hormonal manipulations. The response rates are proportional to the level of hormone receptors measured and the receptor status in the primary tumor probably corresponds, at least to a large extent, to that of any occult metastasis left after surgery.

Since the initial proposal of Schnitzinger in 1889 about adjuvant oophorectomy, there have been over 20 trials of various types of ovarian ablation (19). The earliest endocrine trials were essentially affected by the same defects of many early trials with adjuvant chemotherapy, i.e., historical nonmatched, nonrandomized controls; insufficient information on nodal status. Interpretation of results was further hampered by the absence of adequate statistical methodology for survival analysis. A number of subsequent trials with ovarian ablation, including several prospective randomized studies, showed improvement in both recurrence-free and overall survival rates.

In 1977 the Nolvadex Adjuvant Trial Organization designed the first modern adjuvant trial with the antiestrogen tamoxifen versus control. In a large case series (total, 1131 patients) with node-positive and node-negative breast cancer the 5- and 10-year results provided evidence that total survival was moderately but significantly improved (20). Trials on adjuvant tamoxifen rapidly proliferated among major research centers. In particular, the results of large randomized studies, activated in Europe during the late 1970s, confirmed the benefit of adjuvant tamoxifen especially in women presenting with high receptor-positive tumors (21–23). Despite some inconsistency in published reports concerning menopausal, nodal, and steroid receptor status, over the past decade tamoxifen became widely used in clinical practice, primarily in postmenopausal women presenting with 1–3 positive nodes and ER-positive tumors.

The largest randomized study on adjuvant tamoxifen (total, 2644 patients) was mounted in 1980 by the NSABP group in node-negative and estrogen receptor positive tumors. The 5-year results showed a highly significant \( P < 0.000005 \) reduction in both local-regional and distant metastases. The benefit was observed regardless of menopausal status. However, at 5 years no significant survival advantage could be documented (24).

The International Overview

To assess the impact of various adjuvant systemic treatments (hormonal, cytotoxic, or immune therapy) on total survival, the Early Breast Cancer Trialists' Collaborative Group has set up in 1984 an International Overview with the cooperation of more than 100 individual investigators who have contributed their data. Utilizing proper statistical procedures (25), meta-analysis was conducted on a total of about 30,000 study patients to evaluate the 5-year results (adjuvant treatment versus no adjuvant treatment). When all drug treatments (i.e., single agents as well as various combinations) were considered, meta-analysis detected a significant overall reduction in the odds of death (14%, \( P < 0.001 \)) in favor of the chemotherapy-treated patients. When only CMF-type regimens were considered, the reduction was superior for the total series (23%, \( P < 0.0001 \)), with a 37% reduction in women younger than 50 years old and a 9% reduction for older women. Thus, polychemotherapy was significantly superior to single agents. A similar analysis was carried out on women randomized to receive adjuvant tamoxifen or no tamoxifen. There was an overall reduction in the odds of death of 16% during the first 5 years. Among women older than the age of 50 years, the reduction was 20%.

The updated meta-analysis was conducted on a total of 75,000 women enrolled in 133 randomized trials involving 31,000 (40%) recurrences and 24,000 (32%) deaths. All patients reviewed included 30,000 women in tamoxifen trials, 11,000 in polychemotherapy trials, 15,000 in other chemotherapy comparisons, 3,000 in ovarian ablation trials, and 6,000 in immunotherapy trials (18). Briefly, the findings indicated the following: (a) the long-term (10-year) results essentially confirmed the intermediate (5-year) results, and the cumulative difference in total survival was larger at 10 than at 5 years; (b) longer chemotherapy (e.g., 12 months) was no better than shorter chemotherapy (e.g., 6 months); (c) at the 10-year analysis polychemotherapy was documented to reduce tumor mortality also in 50-year-old women; (d) for the all-ages ER-"poor" (i.e., <10 fmol/cytosol total protein) subset the 10-year mortality reduction following adjuvant tamoxifen was 11% compared to 21% for the ER-"rich" subset; (e) among the 1817 women aged less than 50 years, ovarian ablation was associated with a highly significant improvement in overall survival (25%); (f) adjuvant immunotherapy was unable to influence recurrence-free and overall survival. It is expected that also the updated results of the International Overview will make a considerable impact on clinical practice for they provide a solid confirmation of major individual trials, which already had substituted facts for opinions. The moderate but clinically relevant reduction in tumor mortality could not always achieve the sanctity of statistically significant difference in individual randomized studies. The main reason was essentially lack of statistical power even in major trials accruing 300–400 patients.

The overall validation of benefits from adjuvant systemic treatments reemphasized the importance of previously reported clinical observations underscoring biological concepts. In fact, the highest recurrence rate documented within the first 3–4 years implies a considerable fraction of primary resistant tumor cells, which cannot benefit from the prolonged administration.
of the same polychemotherapy. Also the observation that, following adjuvant tamoxifen, the risk reduction is higher in estrogen receptor-"rich" than in receptor-"poor" assays suggests that tumor heterogeneity plays a major role in treatment outcome. However, in spite of their considerable positive aspects, meta-analyses do not necessarily reflect the state of the art nor should they be expected to provide detailed information to guide physicians in the choice of treatment outside the context of clinical trials, because overviews are not appropriate to answer all specific clinical questions. Besides the above mentioned words of caution, it should be stressed that the most recent trial results with full dose chemotherapy, sequential drug regimens, and role of anthracyclines could not be evaluated in the 10-year overview.

In conclusion, the updated International Overview can provide an adequate average measure of what a practicing physician can expect from adjuvant tamoxifen for the majority of study patients were managed with 20 mg/day for a minimum of 2 years. As far as chemotherapy is concerned, the term "polychemotherapy" comprises a heterogeneous group of treatments delivered through various drugs, doses, and intensity. This remark applies also to CMF, the most widely tested drug combination, although this drug regimen was "the only one with separately demonstrated survival advantage in the present overview" (18).

New Drug Combinations

During the past decade new randomized studies were designed for node-positive breast cancer by major research groups in the attempt to improve the results achieved in the earlier trials. The studies concern the role of anthracyclines in an adjuvant setting and the therapeutic potential of combining chemotherapy and hormones. After 20 years from the first clinical observations (26), Adriamycin (doxorubicin) remains the single most effective drug in the treatment of advanced breast cancer. Once it was clear that the optimal duration of adjuvant chemotherapy could be limited to about 6 months (13), it became almost logical to test whether anthracycline-containing regimens could be more effective than conventional drug combinations also in an adjuvant setting. The biological problem of primary resistant tumor cells in micrometastatic foci was the underlying strategy for the Milan studies. In 486 women with 1–3 involved nodes, i.e., the subset most benefiting from CMF, four cycles of Adriamycin at full dose (75 mg/m² every 3 weeks) were delivered following eight courses of i.v. CMF in the attempt to eradicate CMF-resistant cell lines. At 5 years, the similarity in treatment outcome between CMF and CMF—→Adriamycin suggested the possibility that prolonged administration of full dose CMF actually resulted in the selection of cell-resistant sublines, which were all refractory to Adriamycin (27).

In patients presenting with more than three positive nodes, a different approach was attempted. Adriamycin was administered in both treatment arms either before CMF or alternated with two courses of CMF (28). The superiority of sequential versus alternating regimen is displayed in Fig. 4 for the entire case series (total, 403 cases). When the results were broken down according to degree of nodal involvement, in patients with 4–10 nodes the efficacy of sequential regimen was evident throughout the entire period of observation (Fig. 5). By contrast, in those presenting with more than 10 positive nodes the difference favoring sequential chemotherapy emerged only after the third year (Fig. 6). The findings suggest that in this nodal subset there are patients with tumor cell burden which is so high that even the "best" available conventional regimen will have little, if any, chance to exert effective tumor cell kill on resistant cells. The correct interpretation of reported data is difficult on clinical grounds. A point to be considered is the asymmetrical delivery of drug treatments in the alternating regimen. A clinical trial involves more complexity than any mathematical models may encompass and probably tolerate. Even Goldie and Coldman (29) in their model caution that not every alternating program can be expected to show benefit. If the assumption about lack of symmetry between Adriamycin and CMF is correct, then the advantage of using an optimal sequential schedule rather than an alternating schedule can be substantial.

Other recent adjuvant findings on Adriamycin-containing regimens relate to the studies of NSABP including 1790 cases (30). The marginal advantage, if any, observed by the addition of Adriamycin to melphalan plus fluorouracil or to the same drugs plus tamoxifen is probably due to the low dose (30 mg/m²) of Adriamycin utilized in this study.
The addition of hormonal agents, usually tamoxifen, to adjuvant chemotherapy for resectable breast cancer has received much attention in recent years. The biological rationale for combining these two treatment modalities lies primarily in tumor cell heterogeneity, i.e., various populations of cells with differing sensitivities to chemotherapeutic and endocrine agents. Current adjuvant findings (31) remain inconsistent and controversial because there is not yet a clear evidence from individual trials that the addition of tamoxifen to effective chemotherapy (CMF or CMF-like regimens) has considerably improved treatment outcome versus chemotherapy alone. By contrast, combined chemotherapy and tamoxifen yielded superior treatment outcome versus prolonged adjuvant tamoxifen (3-5 years) in postmenopausal ER-positive tumors (32, 33). The pharmacological reasons remain essentially unproven. In vitro studies have illustrated that endocrine therapies may decrease the cytotoxic effect of chemotherapeutic drugs by altering their cell kinetics (34). This can indeed occur when chemotherapy and hormonal treatments are delivered concurrently. An attractive working hypothesis would be to test the sequential rather than concurrent administration of the two modalities. Relatively short intensive chemotherapy should be given first to kill rapidly proliferating tumor cells; after cytotoxic drugs, tamoxifen should be given for prolonged periods of time to further increase the long-term disease free status.

Chemotherapy for High Risk Node-negative Breast Cancer

For many decades, generations of surgeons believed that histologically node-negative breast cancer represented an almost invariably curable disease. This was a logical consequence of the Halstedian hypothesis of cancer management. About two decades ago, the previously mentioned evaluation of large surgical series (1, 2) began to clearly indicate that the overall 10-year relapse-free survival following radical mastectomy in this patient subgroup was about 70-75%. As in women with node-positive tumors, regardless of tumor size and menopausal status about one-half of all new disease manifestations could be documented within the first 3 years from local-regional treatment and particularly in distant anatomic sites.

In spite of these findings, for at least another two decades surgeons retained the opinion that all node-negative tumors were associated with good prognosis. More recent research efforts, aimed at the identification of new prognostic variables, indicated or reemphasized that in given subsets the distant recurrence rate could be as high as 50%. These clinical findings were in agreement with the previously mentioned hypothesis on the importance of early hematogenous dissemination of cancer cells.

During the late 1980s the reports of a few randomized trials in ER-negative tumors lent considerable support to the strategy advocating a multidisciplinary approach in high risk subsets. The famous Clinical Alert released in May 1988 by the National Cancer Institute, “a poor idea prematurely used” (35) because of too much emphasis on positive treatment findings, served to stimulate physicians and to inform women about the need to reconsider the overall prognosis of node-negative breast cancer and to participate into clinical trials in the attempt to refine patient subsets and treatment outcome.

Fig. 7 illustrates the updated relapse-free and total survival rates of the Milan randomized trial activated in 1980 (11). In spite of the limited number of available patients (total, 90) because of poor referral from surgeons, the advantage of intravenous CMF remains quite evident at 8 years regardless of menopausal status. Premenopausal women given CMF achieved 82% relapse-free survival, while the figure for postmenopausal patients was 76%. Nontreated pre- and postmenopausal controls recorded 8-year relapse-free rates of 40 and 36%, respectively. Also the trend was in the direction of benefit from adjuvant chemotherapy in Grade 3 tumors and in those with high proliferative rate (36).

The magnitude of benefit between control and treated patients was less evident in subsequent large American series (37, 38) although in untreated tumors >3 cm the 5-year relapse rate of the Intergroup trial was 40%. At 5 years or more the treatment arm of the three studies, as summarized in Table 2, yielded comparable results. This finding indicates that combination chemotherapy can effectively reduce the annual odds of recurrence by at least 30% in node-negative breast cancer.

Should all node-negative patients undergo adjuvant systemic therapy? At least for the time being, the answer is no. Although lack of precise rank of available morphological and biological indicators of prognosis renders it somewhat difficult to clearly distinguish between high risk and low risk tumors (39), it does
not make it impossible. The low risk subsets, i.e., women with less than 15% chance of relapse, are usually those with tumors <2 cm in diameter, and/or Grade 1 malignancy, and/or positive steroid receptors (particularly when both ER and progesterone are highly positive), and/or a low proliferative rate. The vast majority of these women can be spared chemotherapy. The converse is true in patients with a potentially high risk of recurrence (something more than 30%) having tumors >3 cm in largest diameter, and/or tumor Grade 3, and/or negative steroid receptors, (particularly when both are negative), and/or high rate of proliferation. If at least two of these unfavorable prognostic factors are present (e.g., large tumor size and high S-phase), adjuvant chemotherapy should be strongly advised. Most probably, patient selection will further improve also by the exhaustive morphological search for axillary lymph node involvement (40) as well as the addition of newer biological indicators.

Prognostic Indicators

Laboratory studies and clinical experience have demonstrated that breast cancer is a highly multiform disease in its pathologic and clinical behavior. Thus, it is not surprising that the clinical course of this malignancy, namely risk of relapse and response to systemic therapy, is often variable. In general, the major determinants of prognosis remain tumor cell burden and drug resistance. During the 1970s the criteria to define high risk patients were nodal status, number of histologically involved axillary nodes, tumor size, and grade. These firmly established prognostic features were later followed by steroid receptor values and tumor cell proliferative activity (thymidine labeling index, DNA ploidy, and S-phase fraction). Since the above mentioned indicators are not, however, absolute, clinicians need additional information that may reflect biological differences to better define tumors associated with poor prognosis. In recent years, biochemical and immunocytochemical variables became the subject of numerous studies. Excessive literature is available on the efficacy of these prognostic indicators, without enabling clinicians to compare the variables with each other and to select the most useful ones among them. The sharpness of $P$ values is not enough to provide complete information. Provisional data from many research groups is still conflicting as to provision of definitive evidence of additional predictive potential compared to conventional prognostic factors.

The constellation of newly proposed variables (e.g., oncogene overexpression, epidermal growth factor receptor, protease calpain D, stress-response proteins, studies utilizing monoclonal antibodies for detection of peritumoral lymphatic and blood vessel invasion to high molecular weight mucin-like antigens) claimed to influence treatment outcome or to help in the treatment decision making remains confusing, and probably disappointing, for the average clinician. In particular, with the possible exception of HER-2/neu protein overexpression in node-positive breast cancer (39), identification of oncogenes as prognostic indicators remains, as yet, of unproved clinical value. In the attempt to correlate laboratory findings with clinical data, a sufficiently large series of consecutive patients, staged and managed according to uniform treatment programs and including information on established prognostic factors, is mandatory. Timing, methods for prolonged follow-up, and proper statistical analysis should further qualify the case series (14, 41). The recent publications on timing of breast cancer surgery during menstrual cycle and its relation to survival of premenopausal women are a case in point. In a retrospective study involving 41 premenopausal women, Hrushesky et al. (42) reported that mastectomy performed during the perimenstrual period was followed by a quadrupled relapse rate compared to that of women operated on during the midcycle. This provocative report implying the influence of chronobiology on a number of clinical events was followed by other similar retrospective

Table 2 Chemotherapy in node-negative breast cancer: results of modern adjuvant studies

<table>
<thead>
<tr>
<th>Selection criteria</th>
<th>Milan</th>
<th>NSABP (37)</th>
<th>Intergroup (38)</th>
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<tr>
<td>Menopausal status</td>
<td>Pre and post</td>
<td>Pre and post</td>
<td>Pre and post</td>
</tr>
<tr>
<td>Tumor size</td>
<td>T1-T3a</td>
<td>Any</td>
<td>T1-T3a</td>
</tr>
<tr>
<td>ER status</td>
<td>Negative</td>
<td>Negative</td>
<td>Negative: all T</td>
</tr>
<tr>
<td>Regimen</td>
<td>C MF iv.</td>
<td>M - F C MF</td>
<td>C MF</td>
</tr>
<tr>
<td>No. of patients</td>
<td>90</td>
<td>737</td>
<td>425</td>
</tr>
<tr>
<td>Median follow-up</td>
<td>8 yr</td>
<td>5 yr</td>
<td>5 yr</td>
</tr>
<tr>
<td>% of relapse-free survival</td>
<td>39</td>
<td>66</td>
<td>61</td>
</tr>
<tr>
<td>Control group</td>
<td>80</td>
<td>78</td>
<td>83</td>
</tr>
<tr>
<td>Chemotherapy</td>
<td>0.0002</td>
<td>0.0007</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

* C, cyclophosphamide; M, methotrexate; F, fluorouracil; P, prednisone.
evaluations (43-45). The results yielded inconsistent findings although they concurred in showing that there was no difference in patient outcome between perimenopausal and midcycle mastectomy. The critical points are not the underlying biological principles (e.g., natural killer cell activities, other immunological or endocrine considerations) or prior laboratory evidence (46) but the risk of drawing treatment indications on the basis of limited retrospective series having inconsistent variables such as stage, follow-up, and adjuvant treatment.

In conclusion, the search for new biological indicators of prognosis, an ever expanding field of investigation, remains important for curious and skeptical clinicians but the novel tissue markers should be handled with care in clinical decision making.

Primary Chemotherapy

The idea of testing the efficacy of primary combination chemotherapy dates back to 1973 (11) when the Milan Cancer Institute started the first prospective study with Adriamycin plus vincristine in locally advanced disease (Stage III). At that time, the aim of chemotherapy was to achieve prompt tumor shrinkage and thus facilitate subsequent irradiation or radical mastectomy. The 10-year results of those studies indicated that the major prognostic factors were tumor cell burden (primary tumor size, clinical nodal status) and adjuvant chemotherapy after local regional treatment (47). These findings were confirmed by American and European research groups utilizing a variety of drug regimens within a similar strategic approach (11).

Two subsequent events have recently brought chemotherapy up front also in earlier disease stages: the similarity of treatment outcome between breast conserving procedures and radical mastectomy in small tumors (48, 49); and both the efficacy and the safety of modern chemotherapeutic (11). The need to decrease the frequency of mutilating surgery in tumors measuring >3 cm led the Milan Cancer Institute to conceive a prospective study with primary (neoadjuvant) chemotherapy in conventionally operable breast cancer (50). The reverse approach, i.e., chemotherapy prior to surgery, could possibly improve long-term results over the classical strategy, i.e., surgery followed by chemotherapy. In fact, in animal models, extensive prior experience has shown that the response to drugs is superior in untreated versus recurrent tumors. The updated results of the Milan study on 227 evaluable patients presenting with resectable breast cancer >3 cm are summarized in Table 3. The degree of tumor response was inversely proportional to the initial tumor diameter and histopathological complete remission was documented in 8 of 220 cases subjected to surgery (4%). Conservative surgery (quadrantectomy plus full axillary dissection) was performed in a total of 201 of 220 (91%). Additional important informations from this prospective study are the following: (a) tumor response was unrelated to the four drug combinations [CMF, FAC (fluourouracil, Adriamycin, cyclophosphamide), FEC (epirubicin substituting for Adriamycin), FNC (mitoxantrone substituting for anthracycline)] with no difference between three and four cycles of either CMF and FAC; (b) three cycles of Adriamycin alone (75 mg/m² every 3 weeks) yielded comparable objective tumor response (79%) as combination chemotherapy (78%); (c) age, menopausal status, labeling index, and DNA ploidy failed to influence the degree of tumor reduction while the frequency of response was greater in receptor-negative tumors. With a median follow-up of 18 months, relapse-free

and total survival rates remain too early to fully evaluate. However, it is important to stress that only 2 local recurrences were detected in 201 patients subjected to conservative surgery plus postoperative breast irradiation.

Drug Dose Intensity and Sequence

Few topics in cancer chemotherapy have received as much attention in recent years as the interrelation of dose, dose intensity, and response. It is well known that the principle of dose response is fundamental to pharmacology. In the medical treatment of cancer, the experimental support for steep dose-response curves is derived from model systems in which a small increase in drug dose results in a disproportionately large increase in tumor cell kill (6, 51-53). In many experimental animal systems the log kill will be greater for the higher dose intensity regimen because that log kill is the difference between cell death and tumor regrowth. The interplay between tumor and drug(s) is actually very complex. Dose response in fact is a property of tumor size, type, proliferative rate, and genetic resistance as well as the differential sensitivity of the normal and tumor cells to the effect of drug(s).

Aside from the initial studies with polydrug regimens for acute leukemia (54) and Hodgkin's disease (8), only during the past decade did clinicians begin to realize that treatment failure could be the consequence of insufficient dose intensity of one or more of the agents in the combination (55, 56). As far as the adjuvant therapy of breast cancer was concerned, the Milan CMF program was the first to provide evidence that outcome at 5 and 10 years was related to full dose treatment (13, 15). In spite of the limitations intrinsic to retrospective evaluations, the findings generated progressive widespread interest on the subject of dose intensity. Dose intensity is actually a concept developed a few years later by Hryniuk (57) and coworkers who emphasized received dose rate rather than total dose received. The concept is complex because it is not just the total amount of drug received, nor is it just the amount of drug received per unit time (e.g., mg/m²/week). It is a mathematical combination of both.

Hryniuk et al. (58, 59) have recently evaluated the relationship between relapse-free survival and dose intensity of CMF adjuvant chemotherapy in node-positive breast cancer. These analyses showed a highly significant relationship between projected dose intensity and 3-year relapse-free survival for studies containing all four subsets of patients (positive nodes 1-3 and >3; pre- and postmenopausal women). Henderson et al. (56) summarized in a review paper the results of retrospective analyses of chemotherapy dose and treatment outcome in adjuvant chemotherapy trials. Although conclusions from data-derived results may be biased, it appears rather clear that the findings of trials refuting the dose-response hypothesis included most of the case series given single agent or low dose combination chemotherapy. Recent prospective randomized trials carried

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**Table 3** Operable breast cancer candidate to mastectomy: clinical versus surgical diameters following 3-4 cycles of primary chemotherapy

<table>
<thead>
<tr>
<th>Initial tumor (cm)</th>
<th>Patients subjected to surgery</th>
<th>Tumor at surgery (cm)</th>
<th>pCR*</th>
<th>Conservative surgery</th>
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<tr>
<td>3.0-4.0</td>
<td>110</td>
<td>93%</td>
<td>11</td>
<td>5</td>
</tr>
<tr>
<td>4.1-5.0</td>
<td>73</td>
<td>79%</td>
<td>10</td>
<td>3</td>
</tr>
<tr>
<td>&gt;5</td>
<td>37</td>
<td>62%</td>
<td>5</td>
<td>73%</td>
</tr>
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* pCR, pathologica complete remission.
out in advanced breast cancer showed that the higher dose of CMF regimens proved to be superior to low dose regimens (60, 61).

Dose-intensive chemotherapy is currently on study within an adjuvant setting when ≥10 axillary nodes are involved. Adopting the concepts of weekly chemotherapy, sequential administration of antimetabolites, and continuous infusion of fluorouracil, Abeloff et al. (62) devised a five-drug regimen to minimize dose reduction and treatment delay. At a median follow-up of 17 months, 8 patients of 53 relapsed. The encouraging therapeutic results (which, however, deserve a longer follow-up observation), manageable side effects, and the authors’ ability to deliver over 90% of the planned doses provide the rationale for a Phase III comparison of this new dose-intensive regimen versus standard chemotherapy.

During the 1980s, the use of high-dose chemotherapy and autologous bone marrow transplantation has been shown to produce rapid and complete responses in patients with advanced breast cancer (63). With the exception of a few women presenting with “small” tumor burdens, sustained complete remissions were limited in number. The main reason for this partial success may be attributed to a high percentage of drug-resistant tumor cells. More recently, the strategy of autologous bone marrow transplantation was focused on the adjuvant setting for women presenting with ≥10 positive axillary nodes. It is expected that in the absence of absolute drug resistance, increasing the dose intensity will increase the log kill and thus improve the clinical results. Table 4 presents the ongoing treatment program of the Milan Cancer Institute. Drug therapy consists of sequential administration of cyclophosphamide, vincristine, and methotrexate plus folinic acid, cisplatin, and melphalan. It is important to point out that because of the hematopoietic stem cell-sparing properties of cyclophosphamide, patients enjoyed benefit from the use of recombinant human granulocyte-macrophage colony-stimulating factor as a means of harvesting by leukaphereses very large quantities of peripheral blood precursors capable of accelerating hematopoietic recovery after subsequent myeloablative chemotherapy (64). Although clinical data are still premature inasmuch as only 48 patients were treated, with a median follow-up period of 21 months the 2-year relapse-free survival is 93%. Present findings appear superior to those achieved with the “best” available adjuvant therapy, i.e., Adriamycin—CMF the 2-year relapse-free survival of which in the subset with ≥10 nodes is 60% (28).

During the past two decades, academic research physicians were influenced in their design of treatment schedules by two strategic models. The Skipper-Schabel hypothesis, derived from experimental animal systems, indicated that for most drugs the log kill increased with increasing dose (5, 6, 51). The Goldie-Coldman mathematical model expanded the horizon by suggesting a new strategy for combining non-cross-resistant drugs in alternating treatment schedules (29, 65, 66). More recently, two distinct conceptual approaches to drug dosing and scheduling were proposed, namely Day’s “worst drug rule” and the “Norton-Simon hypothesis” (67). Both can be considered late intensification strategies, although by completely different lines of mathematical reasoning.

The worst drug rule involves the optimal scheduling of two nonequivalently active drugs (or drug combinations). According to Day, “if drug B is more effective than drug A in the sense of having a larger log kill, then the critical task will be to eliminate the cells that are resistant to B. Since only drug A can do this... every effort must be made to utilize A to the utmost” (67). In other words, in a clinical setting, e.g., adjuvant systemic therapy for breast cancer, research physicians should start with drug (or treatment) A and then switch to the more powerful drug (or treatment B). Does this strategic approach fit well with available clinical findings? Probably yes, only if we suppose that Adriamycin alone is not as active as the combination CMF. However, in some circumstances, as for instance in our trial where four cycles of Adriamycin were followed by CMF (28), the optimum schedule could be represented by starting with the stronger drug and switching very early (68). The explanation offered by Day is that “the scheduling, not the patient group, is responsible for the difference.” The next logical step would be to test the use of single agent Adriamycin. In fact, the recent Milan data on primary chemotherapy for breast cancer presenting with tumor >3 cm (14) clearly indicate that the response rate between CMF and Adriamycin is very similar (73% versus 79%).

Conceptual Modification, Revision, and Evolution

The primary therapy of resectable breast cancer was initiated about a century ago on the principle of centrifugal disease spread along anatomic pathways. Studying the biology of the disease has resulted in the abandonment of the belief that mammary carcinoma always spreads sequentially from the primary site to the nearest draining lymph nodes and then systematically. The adoption of the concept that some cancers may invade the blood stream early to form micrometastases became very helpful in developing several forms of multidisciplinary strategies. The new biological model was followed by successes when correctly applied through prospective randomized trials which, in turn, were capable of generating newer biological concepts, pharmacological strategies, and clinical approaches.

The multidisciplinary strategy has contributed to emphasize the complexity of breast cancer, namely the biological heterogeneity of the primary tumor (69). Tumor heterogeneity has in fact become the major prognostic determinant of treatment selection and outcome and remains the major stumbling block to the cure of a large fraction of patients, even when optimal drug dose intensity is delivered. Our understanding of the interactions between clinical and biological factors and how to construct probabilities for prognosis from these interactions remains incomplete. What we have learned is that the management of the local-regional disease, if done properly by any of a number of methods, does not influence total survival; rather, survival depends primarily on the presence or absence of micrometastases and on the ability of systemic treatment, besides normal defenses of the body, to control their growth.
In the control of distant micrometastases and downstaging large primary tumors to allow easy and safe breast conservation, the contribution of cancer medicine has been substantial (11, 14, 31, 50, 70–73). Available clinical results are far from being optimal, and medical oncologists still must face many failures. However, mortality reductions such as those now demonstrated through meta-analysis at 5 and 10 years can well prevent or significantly delay hundreds of thousands of deaths. Thus, the natural history of resectable breast cancer has been perturbed as a result of the administration of adjuvant systemic therapies and in particular of modern full dose chemotherapy.

Current results should encourage revision of “standard” drug treatments. Improvement in clinical outcome may now be achieved by the delivery of drug dose intensity and the sequential administration of given non-cross-resistant agents. Our own promising and provocative treatment results with Adriamycin followed by CMF should start a revision of prior concepts about optimum delivery of single drugs or combinations of drugs and merit a number of genuine tests in randomized clinical trials. Furthermore, chemotherapy and endocrine therapy are not mutually exclusive. Rather than competing for given patient subsets, they should now become effective partners. Considering steroid receptor heterogeneity, the combined treatment with hormone manipulations and cytotoxic drugs seems rational, because combining both therapies has already shown some additive effect in a few adjuvant studies (32, 33, 74). In fact, given the mixed receptor-“rich” and receptor-“poor” tumor cell populations, improvement in treatment outcome may occur by delivering the two modalities sequentially rather than concurrently. The concomitant administration of both modalities may result in an antagonistic effect due to their specific mode of action (34). One reasonable basis for this antagonism is that antiestrogens probably are cytostatic for cancer cells, whereas certain chemotherapy agents are cell cycle active and thus require DNA synthesis to exert their maximum effect. Therefore, adjuvant treatment should start with chemotherapy, which would affect fast growing receptor-poor cells, and be followed by prolonged administration of endocrine therapy, such as tamoxifen, to keep in check the comparatively slower growing receptor-rich cells.

As far as new drugs and treatments are concerned, probably only taxol (75, 76) holds promises to become a new effective cytotoxic drug in the treatment of breast cancer. This prototype of a novel class of antimitotubule agents that induces excessive polymerization of tubulin has demonstrated significant activity in advanced refractory ovarian epithelial neoplasms and objective responses in various malignancies including breast cancer. Taxol is currently undergoing broad investigation at the Phase II level, but it will take a few years before this novel compound can be taken into consideration for primary or adjuvant treatment in high risk breast cancer. The area of investigation referred to as “biochemical modulation” is the development of strategies that favorably alter the interaction of conventional therapeutic agents with their target end points in both malignant and nonmalignant cells. Therapeutic trials using fluorouracil/leucovorin in refractory and, subsequently, as initial therapy in untreated advanced breast cancer showed encouraging results in the past few years. More recent Phase II trials from Vanderbilt and Baylor Universities (77, 78) using a combination of mitoxantrone with leucovorin-modulated fluorouracil in previously treated metastatic breast carcinoma hold promise for an effective second line chemotherapy. Therefore, comparison with other standard combinations either as first or second line treatment for breast cancer is indicated. Finally, high dose chemotherapy with autologous bone marrow transplantation in an adjuvant setting should be further pursued and refined but within the context of clinical trials. In contrast, current results on biological response modifiers (e.g. α-interferon, lymphokine-activated killer cells, recombinant human tumor necrosis factor) have yielded thus far disappointing or controversial results in the treatment of advanced breast cancer as well as in an adjuvant situation (18). Last but not least, prevention strategies, particularly with tamoxifen, may represent a new treatment approach in healthy women at increased risk for developing breast cancer. European and American investigators concur with the idea that women who are cancer free but who have a clearly defined increased lifetime risk for breast cancer will be eligible for a randomized trial. However, several concerns remain regarding the conduct of such a trial (79).

Changes in biological concepts and treatment results should also favor the most important evolution in clinical practice, i.e., the true multidisciplinary approach to cancer patients. As correctly outlined by Durant (80), proper multidisciplinary teams and environments could provide a cohesive information on management for any given stage of disease. An objective method for decision making would be to discuss with the patient the primary treatment options, whether single or multimodal; whether breast preservation is possible; who should follow the patient; and what the appropriate procedures are. Under broad minded clinical leadership, this team approach would ameliorate the age-old medical practice (“my patient,” “our patients”) and limit the obsession of seeking for second opinions which, too often, yield only conflicting advice.

In conclusion, treatment findings cumulated during the past two decades indicate that modern systemic adjuvant therapies are not a fugitive venture. They are here to stay and to be further improved. Both laboratory and clinical results provided biological and therapeutic models that became very helpful in developing contemporary multidisciplinary strategy and more effective polydrug regimens. The real improvement of prognosis in high risk breast cancer was obtained only by means of clinical trials which were able to validate ideas and theoretical deliberations. The interplay between laboratory research and clinical investigation also confirmed that breast cancer is a highly heterogeneous disease and even single micrometastatic foci can provide a healthy supply of drug-resistant phenotypes. In the future, more efforts should be devoted to selecting or tailoring the “ideal” therapy for each individual case and to properly inform the patients about reasonable treatment alternatives.

References
SYSTEMIC ADJUVANT TREATMENT OF BREAST CANCER


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