The state of the art of adjuvant therapy in breast cancer

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Adjuvant systemic therapy has been shown to reduce relapses in treated women and to prolong their survival. This is true for all studied subpopulations. Multidrug chemotherapy for the duration of 6 months with the addition of tamoxifen for patients with hormone receptor positive tumors and for the premenopausal patients, and tamoxifen or short-term chemotherapy with long-term tamoxifen for the postmenopausal patients represent the treatments of choice to reduce the risk of relapse. In general, patients should be treated with a much more individualized adjuvant therapy program than is currently being prescribed. Current practice is based largely on estimates of average chemotherapy effects obtained from patients with heterogeneous disease and menopausal status characteristics. Some of the open questions relate to i) the definition of the populations for which risk of relapse justifies therapy, and ii) the optimal way of using available therapies might find answer from ongoing research in the next future. The modest but real improvement of the prognosis in operable breast cancer was exclusively obtained by means of clinical trials, and it is mandatory that participation in programs of clinical research become medically and socially the treatment of choice for patients and for their doctors.

Key-words: Adjuvant; breast cancer.

A última palavra em terapia adjuvante para câncer de mama

Estudos têm demonstrado que a terapia sistêmica adjuvante diminui os relapsos em mulheres submetidas a tratamento e melhora a sua sobrevida. Isto se verifica para todas as sub-populações estudadas. A quimioterapia com múltiplas drogas, com duração de 6 meses e adição de tamoxifeno para pacientes com tumores positivos para receptores de hormônios e para pacientes pré-menopausa, e de tamoxifeno ou quimioterapia de curto prazo com tamoxifeno a longo prazo para pacientes pós-menopausa representam os tratamentos de escolha para reduzir os riscos de relapso. Em geral, os pacientes devem ser tratados com programas de terapias adjuvantes mais individualizados do que o que está sendo feito na prática atual. A prática atual é largamente baseada em estimativas de efeitos médios de quimioterapia obtidos com pacientes com doenças heterogêneas e características de quadro de menopausa. Algumas das questões que precisam ser respondidas são: i) a definição das populações de risco para relapso justifica a terapia e ii) a maneira mais otimizada de utilizar as terapias disponíveis poderá ser encontrada nas pesquisas que estarão sendo desenvolvidas em um futuro próximo. A melhora modesta, mas real, no prognóstico de câncer operável foi obtida exclusivamente através de testes

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clínicos. É necessário, ainda, que a participação em programas de pesquisas clínicas seja o tratamento de escolha em termos médicos e sociais para pacientes e seus médicos.

Unitermos: Adjuvante; câncer de mama.

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Introduction

Breast cancer is the most common malignant disease in women; it occurs more frequently in industrialized countries, where its incidence is about 60/100,000 women. At diagnosis, 90% of patients appear to have an operable breast cancer, that is, disease confined to the breast and to the ipsilateral axilla. More than 50% of these patients, however, die of metastatic disease. In fact, once metastases become overt the disease is considered, with very few exceptions, incurable. Since the late forties randomized trials of adjuvant systemic therapy (either endocrine or cytotoxic) have been conducted in an effort to reduce the number of relapses and to prolong the survival of patients with operable disease (1). A recent meta-analysis summarizing the available results of all such trials indicated that the 10-year overall survival absolute benefit varies from 2% to 11%, depending upon age of patients and type of treatments.

Results from randomized clinical trials for women with operable breast cancer indicate that disease-free survival (DFS) and overall survival (OS) may be significantly improved by systemic adjuvant therapy. The most important task today, in addition to procuring a more effective systemic treatment for this disease, is to define those prognostic variables that indicate a lower risk for relapse and thus allow selection of patients who can be cured by local means alone (2). For all others, treatment within clinical trials must become socially and medically acceptable in order to ascertain the best available adjuvant systemic therapy (table 1).

Several prognostic and/ or predictive factors have been identified. These have been classified into patient and tumor factors. The patient characteristic that has been widely recognized as being relevant as a prognostic factor is age. The tumor characteristics widely accepted as prognostic and/or predictive factors are: the size of the tumor, histological tumor type and grade of differentiation, number of positive lymph nodes at presentation, the tumor estrogen and/or progesterone receptor expression and the mitotic rate (NIH Consensus). Of these, the single most important factor is number of involved axillary lymph nodes. Other prognostic factors which have been correlated with worsened outcome and are still under investigation are: overexpression of Her-2/neu, p53 status, vascular invasion and quantitative parameters of angiogenesis.

While in the past the majority of the patients had node positive disease at diagnosis, more sophisticated imaging technologies and the increased awareness of the importance of breast self-examination have significantly increased the proportion of those who present without axillary node involvement. Furthermore, in countries where breast cancer screening programs have been introduced, the percentage of patients with node-negative disease can rise to 80%.

The current hypothesis ascribes the failure to obtain freedom from disease to occult micrometastatic disease already present at the time of diagnosis and first surgery. This hypothesis has acquired indirect support from the results of clinical trials which show no additional advantage in terms of disease-free or overall survival for a more radical local therapy.

Long before the present hypothesis of disease spread (presence of micrometastases at diagnosis), adjuvant systemic therapy was applied in a form of hormonal ablative treatment

Table 1. Adjuvant systemic treatment for patients with operable breast cancer

Risk group	Treatment according to responsiveness to endocrine therapies			
	Endocrine responsive		Endocrine non-responsive	
	Premenopausal	Postmenopausal	Premenopausal	Postmenopausal
Node-negative, "Minimal/Low" Risk	Tamoxifen or none	Tamoxifen or none	Not applicable	Not applicable
Node-negative, "Average/High" Risk	Ovarian ablation (or GnRH analogue) + tamoxifen [± chemotherapy], OR Chemotherapy + tamoxifen [± ovarian ablation (or GnRH analogue)] OR Tamoxifen, OR Ovarian ablation (or GnRH analogue)	Tamoxifen, OR Chemotherapy + tamoxifen	Chemotherapy	Chemotherapy
Node-positive	Chemotherapy + tamoxifen [± ovarian ablation (or GnRH analogue)], OR Ovarian ablation (or GnRH analogue) + tamoxifen [± chemotherapy]	Chemotherapy + tamoxifen, OR Tamoxifen	Chemotherapy	Chemotherapy

GnRH = gonadotropin releasing hormone.
Brackets [ ] indicate questions pending answers from ongoing clinical trials.

consisting of ovarian radiation. At that time, previous observations made of tumor regression after oophorectomy justified investigation of ablative therapy in patients with operable disease after completion of the local treatment.

Systemic adjuvant chemotherapy was based upon observations of substantial rates of response to cytotoxic agents of measurable metastatic disease. In addition, the first hypothesis concerning their value as adjuvant treatment was related to the attempt to kill cells that detach during operation. The detached cells were at that time considered to be responsible for the subsequent development of overt metastases. This hypothesis of perioperative migration of cells with metastatic potential has been abandoned in favor of one that argues for the presence of micrometastatic disease at the time of primary diagnosis (3).

All the knowledge related to the benefits of adjuvant systemic treatment is derived from randomized trials. The trials designed to define treatment benefit in terms of disease-free

survival (DFS) or overall survival (OS) were focused upon the type of therapies that were believed likely to produce an improvement.

Adjuvant chemotherapy

Results from the latest published EBCTCG meta-analysis showed that there was a significant reduction in mortality in patients receiving chemotherapy as compared to patients who did not receive chemotherapy. This benefit was independent of nodal status (negative vs. positive), ER-status (ER -rich vs. ER-unknown or poor), and whether or not tamoxifen was administered. However, the absolute benefit varied according to the patient's age and nodal status. For women under 50 years of age at randomization, combination chemotherapy resulted in a 10-year overall survival absolute benefit of 7% (71% vs. 78%) for node negative and 11% (42% vs. 53%) for node positive. For women who were 50 years or older at randomization, combination chemotherapy resulted in a 10-year overall survival absolute benefit of 2% (67% vs. 69%) for node negative disease and 3% (46% vs. 49%) for node positive disease.

Results from large randomized individual trials are generally in agreement with the conclusions of the meta-analysis (4).

Mechanism of action

The current accepted hypothesis of the mechanism by which adjuvant chemotherapy improves DFS and reduces mortality is that chemotherapy will kill any sub-clinical metastatic disease already present at diagnosis. An additional hypothesis has been postulated to explain the beneficial effect of adjuvant chemotherapy in reducing relapse and mortality in premenopausal patients early during follow-up. The hypothesis is based on whether patients had achieved, or not, chemotherapy induced amenorrhea. Investigations aimed at correlating outcome with amenorrhea in a large population of premenopausal patients gave controversial results (5). While initial investigations on patients in the Milan and the NSABP trials with CMF (78 patients), L-PAM alone, or 5-fluorouracil (96 patients) showed no relationship between amenorrhea and treatment effect, additional analyses, conducted for 1,839 patients from several trials, showed some association between cessation of menses and improved prognosis. The effects of amenorrhea were also seen almost exclusively in the subpopulation of patients with positive estrogen receptors. These observations have led to the speculation that adjuvant cytotoxic therapy is effective only because it causes a chemically-induced oophorectomy (6,7).

Timing

Studying the question of timing of adjuvant chemotherapy has entailed important practical and logistical challenges. Non-randomized presurgical chemotherapy has been studied under a variety of clinical conditions, but has not yielded convincing evidence of benefit greater than that achieved with the established mode of therapy, which is administered only after surgical removal of the primary and axillary nodes for histopathological staging. In a recent series, chemotherapy was given uniformly to patients with large tumors (>3 cm) to reduce tumor size and thus make breast conservation possible. More than 90% of the patients were enabled to have a less-than-mastectomy procedure.

An example of a trial comparing a short course of perioperative chemotherapy is Trial V of the International Breast Cancer Study Group (IBCSG: formerly Ludwig Group) (8). Between 1981 and 1985, 1,275 patients with N- breast cancer received either a single course of cyclophosphamide (C), methotrexate (M) and 5-fluorouracil (F) or no adjuvant therapy. Although the initial benefit in OS and DFS after one perioperative cycle of chemotherapy, observed at 4 years follow-up, was not sustained at 15 years follow-up, there is significant improvement in DFS with PeCT for the postmenopausal patients with ER-negative tumors.

Pre-operative adjuvant chemotherapy

There have been at least six randomized trials investigating the role of neoadjuvant chemotherapy for patients with early

breast cancer.

In the NSABP, the B18 trial was the largest of all these trials. In this trial, patients with stage I and stage II breast cancer were randomized to receive either 4 cycles of anthracycline containing regimen preoperative or the same regimen during the postoperative period. There was a significant reduction in tumor size in about 80% of the patients and a downstaging to N0 in 73% of patients. More patients treated with preoperative surgery were able to have breast conserving surgery, as compared to those patients in the post-operative group (68% vs. 60%). There was, however, no statistically significant difference in DFS or OS in patients receiving pre-operative chemotherapy as compared to those receiving postoperative chemotherapy.

Preoperative chemotherapy may be beneficial in women who desire breast conserving procedures, but who would otherwise not be candidates due to the size of their tumors. However, there is yet no demonstrated clearly statistically significant advantage in DFS or OS for neoadjuvant therapy as compared with adjuvant therapy. In addition, neoadjuvant trials have not addressed the issue of identifying the patients that might require additional chemotherapy after surgery. The challenge remains to identify predictive factors and to identify specific subsets of patients at risk who would benefit from additional systemic therapy. Although neoadjuvant chemotherapy results in a small increase in the rate of breast conserving surgery with similar rates of local control, current neoadjuvant strategies should not replace standard adjuvant therapy.

Timing of initiation of chemotherapy

The question of whether early administration of chemotherapy (immediately after surgery) might improve outcome as compared to the usual delayed administration after removal of stitches and healing of the wound (4-6 weeks) has been asked in a single randomized trial (Trial V of the IBCSG). Trial V showed that no advantage is obtained by starting the adjuvant chemotherapy immediately after surgery compared with the usual delay, provided that six or seven months of adjuvant therapy are administered (7).

Indirect evidence from a study of the Scandinavian Group (9) using a single course of cyclophosphamide alone for 6 days showed that, in all participating hospitals where the drug had been administered immediately after surgery, there was a benefit in favor of the treated patients. In the only hospital in which, due to referral patterns, the treatment started with a delay as short as 3 weeks, no advantage in terms of DFS or OS could be observed.

In addition, the EORTC conducted a meta-analysis that used updated individual patient data from all available randomized trials of perioperative chemotherapy, both published and unpublished. Data on 6,093 patients (1,124 deaths and 1,912 recurrences) from five clinical trials were available (median follow-up duration, 5.3 years; maximum, 11.3 years). No significant effect of PeCT on overall survival was observed. However, patients who received PeCT had a significantly longer disease-free survival (hazards ratio [HR], 0.89; 95% confidence interval [CI], 0.82 to 0.98; $P = .02$).

In conclusion, at present, there is no evidence that PeCT is able to prolong overall survival in patients with early-stage breast cancer; however, further follow-up evaluation is required (10).

The question of timing of chemotherapy has been the subject of interest of the International Breast Cancer Study group. A joint analysis of IBCSG V together with additional IBCSG trials has been performed in an attempt to answer the question of the optimal timing of chemotherapy. The subgroup of patients with estrogen receptor absent tumors who initiate chemotherapy shortly after surgery (within 21 days) have a better disease-free survival than that of patients with estrogen receptor absent tumors who have a delayed initiation of chemotherapy. This is the finding from an analysis of a hypothesis generated by an evaluation of the results from the randomized comparison of six versus seven cycles of chemotherapy among premenopausal women in Trial V, and confirmed by an evaluation of data from Trials I, II, and VI (6).

Duration

Two trials are typical of those that addressed the question of duration of adjuvant cytotoxic therapy. The first is the Milan study of 6 vs. 12 courses of CMF in which 459 N+ breast cancer patients were included. The 10-year results show an advantage in favor of the shorter treatment course (10-year DFS percentage: 46% for the 12 courses as compared to 53% for the six courses). Based upon this trial the proper duration of adjuvant cytotoxic therapy is considered to be six courses (11).

The second trial is related to the hypothesis that the first course, if given perioperatively (immediately after surgery) might yield results in terms of outcome similar to those of the therapies of longer duration. Trial V of the International Breast Cancer Study Group (IBCSG) showed in a population of 1,229 N+ patients that one course of chemotherapy is significantly inferior to the prolonged treatment of 6-7 months in terms of both DFS and overall survival. The search for an "optimal" duration, which, according to the available data, is more than one and perhaps less than 6 courses is ongoing (12).

The EBCTCG meta-analysis confirmed these data by analyzing data from 5 trials comparing duration of at least 6 month to longer duration (9-24months). No survival benefit was demonstrated for duration greater than 6 months.

CMFx3 months versus CMF x 6 months

For the premenopausal patients, a longer duration chemotherapy treatment might be essential to improve results for endocrine nonresponsive disease. Data from Trial VI was evaluated alongside data from another randomized study that was conducted by the German Breast Cancer Study Group (GBSG) to investigate the relative efficacy of 3 versus 6 cycles of CMF chemotherapy. While the initial analyses of Trial VI at five years of median follow-up suggested that three cycles provided insufficient disease control compared with longer duration treatment, the continuing follow-up of Trial VI indicates that the differences between three and six cycles are not statistically significant. The joint analysis of these two trials provided some indirect evidence that 3 courses of CMF might not be enough for very young patients, but provided similar outcome compared with 6 courses for patients over 40 years of age .

Chemotherapy agents

Anthracycline based vs. CMF-based regimens

The EBCTCG meta-analysis analyzed trials comparing anthracycline-based regimens vs. CMF alone. In the latest published EBCTCG there was a small but significant improvement in both DFS and OS for the anthracycline containing regimens.

Several investigators have attempted to improve outcomes by combining anthracyclines and CMF-containing regimens. Results from these studies vary, some showing no advantage with the combination of both regimens and some showing improvement in DFS and OS in the combination arm. The results of these various studies comparing and combining CMF- and anthracycline-containing regimens suggest a slight advantage for the latter in both pre and postmenopausal women. However, it remains uncertain whether there is a benefit in combining both regimens. There is some suggestion that predictive factors could be used in the assessment of response of anthracycline-containing regimens. There is some retrospective data showing that tumors overexpressing Her2/neu would respond better to anthracycline containing regimens. However, because of the retrospective characteristic of these data and because, at present, the optimal method of measuring HER2/neu remains controversial, the use of Her2/neu overexpression as a predictive factor remains investigational.

Dose intensity and high-dose chemotherapy

Several trials have explored the use of high-dose chemotherapy. Neither escalating doses of cyclophosphamide (NSABP B-22 and B25), nor the escalation of doxorubicin (CALGB

9344) have shown any advantage over the standard dose treatments. Several clinical trials have tested high-dose chemotherapy with bone marrow transplant or stem cell support in women with 4 or more positive lymph nodes. Preliminary reports, published in abstract form only, from two clinical trials comparing conventional chemotherapy to high-dose chemotherapy with bone marrow transplant or stem cell support in high-risk patients in the adjuvant setting indicate no overall or event-free survival benefit from the high dose chemotherapy . One small trial, also published only as an abstract, showed a statistical survival benefit of high-dose chemotherapy when compared to conventional dose chemotherapy . It is now known that the results from this latter trial are based on fraudulent data. Rodenhuis et al. recently presented the preliminary results of a randomized trial comparing standard chemotherapy to standard chemotherapy followed by high dose chemotherapy with peripheral blood progenitor cell transplantation for patients with 4 or more positive nodes. Although the preliminary results showed a benefit for the high dose arm, longer follow-up of this study should be awaited.

IBCSG 15 was conceived with a slightly different schema in which high-dose patients were randomized to upfront 3 cycles of high-dose chemotherapy vs. conventional chemotherapy. The result of some of these studies and further follow-up on others will help clarify the role, if any, of high-dose chemotherapy in the adjuvant setting. Because, at present, there is no convincing evidence to demonstrate that high-dose chemotherapy with stem cell support results in improved outcomes compared to standard polychemotherapy regimens, this treatment strategy should not be offered outside clinical trials.

Other chemotherapy regimens

Recent trials are exploring the addition of taxanes in the adjuvant setting. The U.S. Intergroup Study compared AC with or without sequential paclitaxel in 3170 women with node-positive disease. An initial report of this study at 21 months follow-up showed a small but significant advantage in both DFS and OS in the taxane treated cohort (reduction in risk of recurrence of 22% and in risk of death of 26%). At 30 months follow-up, these differences persisted and this served as the basis for the approval of paclitaxel for the adjuvant treatment of breast cancer patients by the FDA. A letter to Lancet at that time questioned whether there was enough evidence to support the use of paclitaxel after doxorubicin/cyclophosphamide in the adjuvant therapy of node-positive breast cancer (13). A subsequent report on this study at 52 months median follow-up showed results had significantly changed since the original report: the difference in overall survival observed initially favoring the paclitaxel arm is no longer statistically significant (P =0.0745). The benefit in the risk of recurrence and death from the addition of paclitaxel to AC has decreased to 13% and 14% respectively. In addition, when subset analysis were performed, patients with ER-positive tumors and who received 5 years of tamoxifen experienced no benefit from the addition of taxol.

A second trial which looked at the same question was NSABP B-28 in which 3060 patients with node-positive breast cancer were also randomized to AC with or without sequential paclitaxel. At 34 months follow-up, there were no statistically significant differences in either DFS or OS between both treatment groups.

Major differences between these two similar trials that had preliminary dissimilar results were found in the number of positive nodes: in the NSABP trial 70% patients had 1-3 positive nodes, while in the Intergroup trial only 46% had 1-3 positive nodes.

Because of the lack of consistency among the results currently available, recently completed and ongoing trials of taxanes in the adjuvant setting will be needed to define the value of taxanes in the treatment of early breast cancer.

Endocrine therapy

Who should receive tamoxifen?

The most recently published ECBTCG meta-analysis included information on 37,000 women with stage I or II breast cancer in 55 trials of adjuvant tamoxifen. In this analysis, the

benefit of tamoxifen was found to be restricted to women with ER-positive or ER-unknown tumors (14). The 10-year reduction in recurrence and mortality after 5 years of tamoxifen were of 45% and 26% respectively. Additional data regarding tamoxifen use in women with ER-negative tumors will be available from the NSABP B-23 trial. The benefit of tamoxifen for patients with ER-positive tumors was independent of age, menopausal status, involvement of axillary lymph nodes, or tumor size. This meta-analysis confirmed the benefit of adjuvant tamoxifen for ER-positive premenopausal women to be similar to that for postmenopausal women. In addition, the proportional reductions in both recurrence and mortality associated with tamoxifen use were similar in women with either node-negative or node-positive breast cancer, but the absolute improvement in survival at 10 years was greater in the latter group (5.6% vs. 10.9%).

Adjuvant hormonal therapy should be recommended only to women whose breast tumors express hormone receptor protein regardless of age, menopausal status, involvement of axillary nodes, or tumor size (NIH consensus).

ER determination

Selection of appropriate adjuvant treatment for women with breast cancer requires information about the ER content of the primary tumor. The ER determination should be performed in a well- established, skilled laboratory. Immunohistochemical assays appear to be at least as reliable as standard ligand-binding assays in predicting response to adjuvant endocrine therapy (15).

Dose

The dosage of adjuvant tamoxifen has not been studied. Doses between 20 mg and 40 mg a day have been given in various trials. An excess of endometrial cancer in patients who received 40 mg a day for at least 2 years previously reported, could not be confirmed in an analysis of the Scottish trial in which 20 mg a day were given for 5 years. Assuming equivalent antineoplastic effectiveness for these two doses of tamoxifen, the recommended dose is therefore 20 mg a day.

Duration of tamoxifen

The optimal duration of tamoxifen has been addressed by the EBCTCG meta-analysis and by several other large randomized trials. Results from the EBCTCG meta-analysis show a highly significant trend towards greater effect with longer treatment (1 year vs. 2 years vs. 5 years). The proportional mortality reductions were 12% for 1 year, 17% for 2 years and 26% for 5 years. The NSABP B-14 study, which compared 5 years to 10 years of adjuvant tamoxifen for women with early stage breast cancer, indicated no benefit for continuation of tamoxifen beyond 5 years in women with node-negative, ER-positive breast cancer . The Scottish Group conducted a similar trial but for women with both node-positive and node-negative disease, and found no benefit for 10 years of tamoxifen over 5 years of treatment. In both trials there was a trend towards a worse outcome associated with a longer duration of therapy. The ECOG trial randomized node-positive women who had already received 5 years of tamoxifen following chemotherapy to either continue treatment or observation. In the ER-positive subgroup, there was an increase in DFS associated with prolonged tamoxifen use, but no impact on overall survival.

The optimal duration of tamoxifen treatment for node-positive women is still controversial and is being studied in ongoing or recently closed clinical trials. Therefore, standard adjuvant treatment is currently 5 years of tamoxifen.

Ovarian ablation

The EBCTCG has performed a meta-analysis of 12 trials of ovarian ablation (by radiation or surgery) in women with early stage breast cancer. The meta-analysis included trials of ovarian ablation vs. no therapy and ovarian ablation plus chemotherapy vs. the same chemotherapy alone (16). There was a significant improvement in the overall 15 year survival in the ablation group among premenopausal women (6.3% absolute

reduction in mortality) but, as expected, not in the postmenopausal group. As with tamoxifen, the proportional benefit was similar in node-negative and node-positive patients, but the absolute survival benefit was larger for the latter group. The ER status was not known for the women who participated in the early trials of ovarian ablation alone. In trials comparing ablation plus chemotherapy vs. chemotherapy alone the benefit of ablation was seen only in the ER-positive subgroup.

There is recent data about trials using LHRH agonists and comparing this to other treatment modalities.

LHRH agonists alone

The preliminary results of the ZEBRA trial were recently presented. This was a large (1,640 patients) randomized, multicenter trial comparing the effect of goserelin vs. CMF in pre/perimenopausal patients younger than 50 years old with node positive early breast cancer. After a median follow-up of 6 years, goserelin was found to be equivalent to CMF in terms of DFS in ER-positive patients (HR=1.01). For ER-negative patients, there was a significant advantage in favor of CMF in terms of DFS (HR=1.75, 95%CI=1.27-2.44). Data on OS is not mature yet. Results from other ongoing or recently closed trials like IBCSG VIII comparing LHRH agonists to other treatment modalities will provide additional valuable information.

LHRH agonists plus tamoxifen

The Austrian Breast Cancer Study Group (ABCSG) conducted a trial (AC05) comparing goserelin plus tamoxifen in 1045 premenopausal patients with ER/PgR-positive early breast cancer. At a median follow-up of 42 months, a significantly improved recurrence-free survival was observed with Zoladex and tamoxifen combination therapy compared with CMF therapy (p=<0.02). This trial has been criticized as the CMF arm did not receive tamoxifen, and thus it is unclear whether the benefit is achieved by LHRH agonist, tamoxifen, or the combination of both.

Another trial conducted by the Italian Breast Cancer Adjuvant Study Group (GROCTA 02) was deigned to answer the same question with a similar trial design. Pre/perimenopausal patients with ER-positive early breast cancer (n=244) were randomized to CMF chemotherapy versus ovarian suppression plus tamoxifen. Ovarian suppression could be achieved by radiation therapy, oophorectomy, or LHRH agonist. Results at a median follow-up of 76 months revealed that tamoxifen plus ovarian suppression achieved similar results in terms of DFS and OS to those of CMF, regardless of nodal status. Furthermore, there was no difference in clinical outcome of patients treated with oophorectomy or ovarian irradiation compared with those treated with LHRH agonist.

LHRH agonist in addition to standard therapy

A combined analysis of four trials recruiting 2,648 premenopausal patients collaborated to the ZIPP trial to investigate the effect of adding an LHRH agonist to standard therapy in premenopausal patients with early breast cancer, regardless of nodal or ER status. Patients were randomized to receive LHRH agonist, tamoxifen, LHRH agonist plus tamoxifen, or no further treatment after standard treatment (surgery and/or radiation therapy and/or cytotoxic chemotherapy and/or tamoxifen). The ZIPP trial results showed a significant improvement in recurrence-free survival for patients receiving LHRH agonist (RR=0.77, 95%CI 0.66-0.89; p<0.001) compared to those not treated with the LHRH agonist.

LHRH agonist +/- tamoxifen following cytotoxic therapy

Three American groups (ECOG, SWOG and CALGB) joined forces in an intergroup trial (INT-0101) to compare CAF vs. CAF followed by LHRH agonist either alone or with tamoxifen in premenopausal patients with node positive, hormone receptor positive breast cancer. There was a significant improvement in 5-year DFS for the CAF/LHRHagonist/tamoxifen group (77%) compared with patients treated with CAF/

LHRHagonist (70%) with a trend towards improved 5-year DFS for CAF/LHRHagonist vs. CAF (p = 0.06).

LHRH agonist alone or in combination with cytotoxic chemotherapy

In IBCSG VIII premenopausal women (n = 1,096) with node-negative early breast cancer were initially randomized to CMF alone, CMF followed by LHRH agonist, LHRH agonist alone, or no further treatment. The no-treatment arm was subsequently dropped because evidence from other trials showed that adjuvant treatment improved outcome. An analysis of the effect of adjuvant treatment vs. no adjuvant treatment in this trial has confirmed that adjuvant treatment improves outcome in premenopausal patients with node-negative early breast cancer. Further results from this trial are awaited.

The results from the ZEBRA trial have shown that LHRH agonists is equally effective as CMF in premenopausal patients with ER-positive tumors. The AC05 and GROCTA 02 trials have demonstrated that LHRH agonist combined with tamoxifen is at least as effective as CMF again in prenemopausal patients with hormone receptor-positive tumors. The ZIPP trial has demonstrated that the addition of LHRH agonist to standard therapy is beneficial. Also the INT-0101 trials has shown that the addition of LHRH agonist, alone or in combination with tamoxifen, to CAF is beneficial in patients with hormone receptor tumors. In summary, LHRH agonists alone or in combination with standard therapy provide another choice of treatment for premenopausal women with hormone-receptor positive tumors.

The question that still remains unanswered is what is the benefit of the addition of chemotherapy to combined hormonal treatment. IBCSG 11-93 was designed to randomize premenopausal women, with node positive, hormone responsive tumors to ovarian ablation and 5 years of tamoxifen with or without chemotherapy. After accruing only 174 patients, the study had to close early due to low accrual as investigators were reluctant to randomize this subset of patients to a non-chemotherapy arm. The question addressed in this study still remains unanswered and similar trials should be planned to answer this important question.

The question of whether ovarian ablation adds to the effect of chemotherapy in premenopausal women has also been examined by the EBCTCG meta-analysis. The benefit of ablation appeared to be less in the group of women who also received chemotherapy, although this subgroup was small. Preliminary results from a study of 1500 patients, indicated that LHRH agonist goserelin did not improve 5-year overall survival when added to adjuvant CAF (cyclophosphamide, doxorubicin, 5-fluorouracil), with or without tamoxifen.

Aromatase inhibitors

Third generation oral aromatase inhibitors have clearly been accepted as secondline hormonal treatment of metastatic hormone dependent breast-cancer, and most recently accepted as first line treatment in some other countries. Several studies are addressing the role of third generation aromatase inhibitors in the adjuvant setting. Two strategies of using aromatase after or combined with tamoxifen are being evaluated in postmenopausal patients with hormone responsive tumors. The MA.17 international intergroup trial is randomizing patients who are disease-free after 5 years of adjuvant tamoxifen to an additional 5 years of letrozole or placebo. In a similar design, the NSABP B-33 randomizes patients to 2 years of exemestane or placebo after a standard 5 years of adjuvant tamoxifen. The second approach to use aromatase inhibitors in combination with tamoxifen is the use of both agents in sequence within the first 5 postoperative years. The ICCG is comparing 2 years of exemestane after 3 years of tamoxifen to a standard 5-year course of tamoxifen. Similarly, the ARNO trial is comparing 5-years of tamoxifen vs. 2 years of tamoxifen followed by 3 years of anastrozole. In the four-arm BIG1-98 study, being coordinated by IBCSG, patients are randomized to one of the 4 following arms: 5-years of tamoxifen, 5-years of letrozole, 2 years of tamoxifen followed by 3 years of letrozole, or 2 years of letrozole followed by 3 years of tamoxifen. A slightly similar strategy exploring the combination of tamoxifen with aromatase inhibitor is explored in the ATAC trial. This trial, which has recently closed accrual, compared 5 years of tamoxifen

vs. 5 years of anastrozole vs. the combination of both. The results of this trial will also provide useful information in this area.

Chemoendocrine

Combined chemoendocrine therapies have been the subject of many trials, most of which are either too small to be conclusive or have too brief a follow-up. The rationale for combining the two modalities was the possibility of finding synergistic or additive effects on tumor cells. The two therapies have different spectrums of toxicity that facilitate their simultaneous use.

Many trials have been reported showing that adding chemotherapy to tamoxifen might be beneficial for postmenopausal patients with ER-positive tumors. The majority of these trials were conducted exclusively in patients with node-positive disease. In NSABP-B16, women of 50 to 59 years of age with node positive tumors and women 60 years of age and older, irrespective of Er and PgR status were randomized to tamoxifen alone vs. chemotherapy (doxorubicin and cyclophosphamide) and tamoxifen. Again, there was a significant improvement in DFS and OS for the combination arm (17).

Two large studies have asked the same question in the node negative population. In the NSABP B-20 patients with node-negative, ER-positive breast cancer were randomized to tamoxifen alone vs. chemotherapy (CMF or sequential methotrexate and 5-FU). plus concurrent tamoxifen. At 5-years of follow-up, there was a statistically significant advantage in both DFS and OS for the combined arm. However the benefit was greater in women younger than 50 years of age. IBCSG IX randomized node negative, postmenopausal women to tamoxifen alone vs. chemotherapy followed by tamoxifen. Initially the trial included ER- negative as well as ER-positive tumors. This study showed a significant advantage only in DFS for the combined arm. However, no significant advantage for the addition of chemotherapy for postmenopausal women was found in the ER-positive cohort (18,19).

The role of adding chemotherapy to tamoxifen for postmenopausal, ER-positive, node negative patients is still controversial.

Treatment of elderly patients

Breast cancer in the elderly is a considerable public health problem. About 45% of all newly diagnosed breast cancers are estimated to occur in women above the age of 65. In this age group the yearly incidence rate of breast cancer is estimated to exceed 320 per 100,000 population. Co-morbid conditions and compromised functional status are usually the basis for the tendency to exclude the elderly from randomized clinical trials . Proposals have been made to treat elderly patients with tamoxifen alone and no surgery. This approach has unacceptably high local failure rates and outside a clinical trial setting should be used only for patients who are not candidates for surgery or those who refuse it. Guidelines for treating elderly patients are usually extrapolated from results of trials conducted in a younger population. However, a recent survey showed that in terms of survival, elderly women do as well as younger patients for locally and regionally-confined disease stages, but far worse for distant metastatic disease. Data are available from three trials in which the elderly were specifically treated with an endocrine therapy . These data represent the basis for the treatment recommendation in this age group.

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