Controversies in Breast Cancer

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Clinically relevant issues are yet to be resolved in many aspects of breast cancer management.

Background: A large number of controversies about the management of breast cancer produce uncertainties for patients and physicians alike. In addition, questions are constantly raised about the true value of new approaches or treatments.

Methods: The authors have conducted a critical review of the literature on several of these issues, and they present a balanced view that can be useful for clinical decision making.

Results: Although new staging systems for ductal carcinoma in situ have been proposed, a consensus has not yet been reached regarding the criteria to allow tumor excision alone. The extent of benefit of the main adjuvant therapies is becoming better established, and improvement in outcomes may accrue from dose-intensive treatments and autologous stem cell or hematopoietic growth factor support.

Conclusions: Progress in breast cancer management continues to evolve. Several new approaches either reduce morbidity or improve outcomes.

Introduction

The presentations and management of patients with breast cancer have changed markedly over the last several decades. In the 1960s and earlier, patients were often hospitalized with recurrent disease and massive arm lymphedema years after their radical mastectomy and postoperative radiotherapy, and their responses to palliative hormones or chemotherapy were only temporary. Today, a significant percentage of patients present with noninvasive breast cancer detected mammographically, and even those who have invasive disease often have a small primary tumor with negative ipsilateral axillary lymph nodes. Despite this shift in clinical presentation, many controversies remain regarding management of women with early breast cancer, with more advanced local tumors, and with regional spread or metastases. This review highlights conventional treatment results and discusses some of the controversial issues surrounding these approaches. Table 1 presents an overview of the controversies associated with treating patients with breast cancer.

Table 1– Controversies in Breast Cancer

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The principal reason for the controversies is the lack of definitive outcome data on most of the newer promising methods that have been applied to a group of diseases, all with inherently long and variable natural histories. In the absence of well-controlled, prospectively randomized clinical trials of sufficient size to exclude a spurious positive result occurring by chance alone, most newer treatments being used today should be viewed as “a hope and a promise” rather than as accepted replacements.
for conventional approaches. When viewed in this context, the following discussions address unresolved issues on a particular disease aspect rather than true controversies in management.

**Surgical Issues**

Unresolved surgical issues include mastectomy indications, selection of lumpectomy alone, clinical relevance of comedonecrosis and nuclear grade, and the role of sentinel node biopsy in influencing the need for axillary dissection.

**Ductal Carcinoma In Situ**

The incidence of ductal carcinoma in situ (DCIS), particularly the type detected by microcalcifications in a mammogram, is increasing. In 1992, DCIS represented approximately 12% of all new breast cancer diagnoses and accounted for 40% of mammographically detected breast cancer. Several controversial issues have arisen, including the identification of significant histopathologic features, the importance of surgical margins, the use of local treatment options, and the role for systemic therapy. Total mastectomy and lumpectomy with radiotherapy are the standard treatment options. Lumpectomy with radiotherapy with or without tamoxifen is under clinical evaluation. Axillary node involvement in DCIS is rare; thus, node dissection is rarely indicated.

Overall, the long-term outlook for DCIS is excellent. While more than 98% of women are cured by total mastectomy, this may not be the most appropriate option for treatment of DCIS today. Several series from single institutions demonstrate that selected patients have a low ipsilateral recurrence rate following local excision alone. Pathologists debate over how to best identify low-risk DCIS lesions. Several pathologic staging systems have been developed and tested retrospectively, but consensus recommendations have not yet been reported. Part of the problem stems from the fact that there are several histologic subtypes of DCIS, including micropapillary, papillary, solid, cribriform, and comedocarcinoma. Comedocarcinoma is often more aggressive and is associated with a higher probability of microinvasion.

The selection of treatment also can be controversial when there is initial margin involvement by tumor. Reexcision is indicated if the margin is positive, and the total extent of disease is evaluated before proceeding with radiotherapy or mastectomy. Mastectomy has been the usual treatment choice for patients with persistent microscopic involvement of margins after local excision and for those with a diagnosis of DCIS and evidence of suspicious, diffuse microcalcifications. Two elements needing more precise definition are (1) the early identification of the woman who would best be treated with mastectomy and (2) the selection of the woman who can be treated adequately with local excision alone. The local recurrence rate for lesions smaller than 25 mm with low nuclear grade and no evidence of comedonecrosis is only 2.3%. In comparison, the local recurrence rate for high-grade DCIS with comedonecrosis is 33%. Lagios et al highlighted the importance of nuclear differentiation and the presence or absence of comedonecrosis in identifying women at higher risk of recurrence after local excision alone. Simpson and Page emphasized the heterogeneous nature of DCIS and the need for clear surgical margins. For patients with DCIS treated with breast conservation, Silverstein et al have proposed a prognostic classification consisting of three risk groups: non-high grade DCIS without comedo-type necrosis, non-high grade DCIS with comedo-type necrosis, and high-grade DCIS with or without comedo-type necrosis.

Local excision plus radiation is often recommended for women who are not treated with total mastectomy for DCIS. In those women who have a recurrence after conservative therapy, their survival is comparable following salvage mastectomy. The National Surgical Adjuvant Breast and Bowel Project (NSABP) B-17 protocol involving 790 women reported that radiation reduced the occurrence of second ipsilateral breast cancers from 16.4% to 7.0% overall. No survival advantage was observed, however, since most recurrences could be managed by salvage mastectomy. Solin et al reported a local failure rate of 19% after 12 years of follow-up following local excision plus radiation, including 55% with invasive cancer and 45% with DCIS. The cause-specific survival was 96% at 12 years.

Thus, the optimal strategy for local management of DCIS remains unclear. The possible benefit of tamoxifen in DCIS treated by lumpectomy with or without radiation is being evaluated in the ongoing NSABP B-24 study.

**Lobular Carcinoma In Situ**

Lobular carcinoma in situ (LCIS) typically is diagnosed only after a biopsy is performed for another suspected breast abnormality. Its pattern may be focal but distributed throughout the breast, and LCIS is often bilateral. The chance of developing an invasive cancer is 25%. LCIS may be either infiltrating lobular or, more commonly, infiltrating ductal carcinoma. The management of patients with LCIS is controversial, with options ranging from no treatment after biopsy except follow-up by both physical examination and mammography to bilateral prophylactic mastectomies. There is no role for tamoxifen for LCIS.

**Invasive Breast Cancer**

The role of sentinel node biopsy and the identification of patients who routinely might not require axillary node dissection are unresolved surgical issues for early invasive breast cancer. These are discussed elsewhere in this issue. Whether the highly specialized technique of selective lymphadenectomy can be widely applied by many different surgeons and whether its widespread use will impair survival rates achieved with axillary dissection remain unclear.

**Radiation Therapy Issues**

Several controversial topics related to indications for radiation therapy include its use in low-risk DCIS patients treated by lumpectomy, postmastectomy radiation therapy for node-positive breast cancer patients, and the timing of radiation and chemotherapy in patients who have undergone a partial mastectomy for invasive breast cancer. Discussions regarding radiation therapy issues are presented elsewhere in this issue.

**Adjuvant Chemotherapy Issues**

Local therapies for breast cancer (eg, partial mastectomy, axillary node dissection and radiation to the remaining portion of the breast, modified radical mastectomy) are recognized and accepted. A number of chemotherapy issues have yet to be resolved, despite more than two decades of clinical trials in the modern era of adjuvant chemotherapy for breast cancer. Some of these issues include comparisons of cyclophosphamide, methotrexate, and fluorouracil (CMF) vs doxorubicin in adjuvant therapy and in metastatic disease; drug sequencing; dose considerations; and the introduction of promising new agents in node-positive patients.
Based on an overview analysis of 75,000 patients enrolled in 133 randomized clinical trials, postoperative systemic adjuvant therapy for breast cancer suggests that a survival advantage occurs in premenopausal patients treated with CMF chemotherapy for six months and in postmenopausal women treated with tamoxifen for at least two years. CMF provides a 25% reduction in mortality at 10 years, or 12 additional lives saved for every 100 patients treated, and tamoxifen results in a 20% reduction in mortality, with 10 additional lives saved for every 100 patients treated. Oophorectomy is also effective in premenopausal patients. These results for node-positive patients confirm recommendations from two earlier National Institutes of Health Consensus Development Conferences but no therapeutic recommendations for node-negative women were given in a later conference. This meta-analysis has been updated with 15-year results (Table 2). Formal presentations of the data indicate an overall annual reduction in mortality risk by chemotherapy of 18% ± 3%, including a 27% reduction in mortality for node-negative patients and a 14% reduction for node-positive patients. Patients 50 years of age or older had an 11% reduction in mortality, and those who were 70 years of age or older had no benefit from chemotherapy. In contrast, women 50 years of age or older who were estrogen receptor (ER)-positive had a 27% ± 5% mortality reduction with tamoxifen, and those under age 50 years had a 14% ± 3% overall reduction. There is no beneficial effect from tamoxifen in estrogen receptor-poor patients of any age, but tamoxifen plus chemotherapy leads to an additional 12% reduction in mortality for patients with ER-positive tumors. Oophorectomy affords a 16% ± 5% mortality reduction in women under 50 years of age but has no effect in patients who are 50 years of age or older.

**CMF vs Doxorubicin-Based Regimens**

CMF is considered the "gold standard" for adjuvant combination chemotherapy, but other familiar combinations may offer similar therapeutic benefit, although not all have been compared with an untreated control group in prospective, randomized trials. These include cyclophosphamide plus doxorubicin (CA), cyclophosphamide, doxorubicin, and fluorouracil (CAF), and cyclophosphamide, methotrexate, fluorouracil, vincristine, and prednisone (CMFVP). CA may be given with or without tamoxifen.

Although CMF is the "gold standard" for premenopausal women whose prognostic risk assessment make them candidates for chemotherapy, many cooperative group protocols are using CAF or CA as the control arm, and many patients not on trial are treated with a doxorubicin-based combination. While most oncologists would agree that six cycles of CMF are as effective as 12 cycles, many issues are unclear. Is a regimen of intravenous CMF every three weeks equivalent to the original CMF reported by Bonadonna et al? Is cyclophosphamide necessary? Is methotrexate plus fluorouracil just as effective? Is CAF or CA superior to CMF? Does sequencing of CMF with an anthracycline make a difference in long-term outcome, and is this a better strategy than using any single combination?

Published data comparing the efficacy of CMF with doxorubicin-based chemotherapy for metastatic disease and as adjuvant therapy are inconclusive. While studies often demonstrate a more favorable response rate in metastatic disease with the anthracycline regimen, it is unclear whether this is due to the types (bone/visceral vs soft tissue) and numbers of patients studied, the study design (intravenous vs oral cyclophosphamide), the number of various drugs and dosages in each arm, the length of follow-up, or other factors. In adjuvant therapy, most of the same issues apply. The Cancer and Leukemia Group B (CALGB) study reported a positive effect when doxorubicin was substituted for methotrexate in the "Cooper regimen" (CMFVP). A recent report with a 16-year median follow-up compared CMF with cyclophosphamide, doxorubicin, fluorouracil, and vincristine (CAFV) and showed significant overall and disease-free survival with CAFV. Unfortunately, this trial does not resolve the question since there were several variables between the two arms, including doses of cyclophosphamide and fluorouracil, routes of cyclophosphamide (intravenously in CAFV and orally in CMF), use of radiotherapy in only 55% of the total 249 patients, and unexplained differences in outcome related to menopausal status and the number of involved nodes. A newer trial with a five-year follow-up shows no difference between CMF and CAFV if given in equitoxic doses.

Many other adjuvant chemotherapy issues remain unresolved. Should chemotherapy be different in node-positive vs node-negative women or in premenopausal vs postmenopausal women? Can newer agents (e.g., the taxanes, vinorelbine, platinum, topoisomerase-I inhibitors) replace or be incorporated into conventional adjuvant chemotherapy? Many early reports suggesting a divergence in the natural history of a particular disease subset by a new treatment approach seem to pale with longer follow-up as survival curves merge.

**Node-Positive Breast Cancer Patients**

Unresolved issues regarding the management of node-positive breast cancer include the identification of better treatment programs for premenopausal women, the use of postmenopausal chemotherapy, and the role of high-dose strategies for high-risk patients, using either bone marrow transplant or peripheral blood stem cell support following ablative doses of chemotherapy or colony-stimulating factor (CSF) support after dose-intensive regimens. Clinical trials addressing these areas are underway to assess both efficacy and toxicity, since recent findings have noted an increased incidence of endometrial cancer after tamoxifen use and acute leukemia or myelodysplasia after high-dose cyclophosphamide treatment. One Intergroup trial (INT0101) in premenopausal, receptor-positive, node-positive patients is comparingCAF chemotherapy alone for six cycles to sequential CAF followed by goserelin acetate for five years to sequential CAF followed by combined tamoxifen and goserelin acetate for five years. Another Intergroup trial (INT0100) in the same type of postmenopausal patients is comparing standard adjuvant tamoxifen alone for five years to sequential CMF for six cycles followed by tamoxifen to concurrent chemoendocrine CAF plus tamoxifen for six cycles, then tamoxifen to a total of five years. Thus, the control arms are CAF chemotherapy for the premenopausal trial and tamoxifen for the postmenopausal trial, but both studies involve patients who are ER-positive. A trial (S9313) for patients with up to three positive nodes is evaluating CA in high doses given together or sequentially. Doxorubicin sequence may be an important determinant of outcome. As noted recently, four cycles of doxorubicin preceding eight cycles of CAF was more effective than alternating CAF for two cycles and doxorubicin for one cycle for 12 courses.

**New Agents**

New chemotherapeutic agents are now available for breast cancer treatment. The most mature of these are the taxanes, paclitaxel and docetaxel, but vinorelbine and the camptothecans, topotecan and irinotecan, also have activity in metastatic breast cancer. The taxanes have shown impressive single-agent activity in treating metastatic disease, as first-line chemotherapy as well as in patients previously treated with an anthracycline. Paclitaxel is being evaluated as a sequential treatment in a trial (C9344) for node-positive patients who are receiving CA, with doxorubicin given at either standard or dose-escalated levels. Gianni et al reported that the combination of 125 to 200 mg/m² of paclitaxel given over three hours with 60 mg/m² of doxorubicin as first-line chemotherapy achieves
Dose Delivery and Effects

Dose schedule is an unresolved issue with paclitaxel. The NSABP B-26 protocol is studying the issue of three-hour vs 24-hour administration of paclitaxel in metastatic breast cancer. No comparative trials in breast cancer have been reported that address the remaining questions concerning other dosage schedules. The dose of paclitaxel presents another issue, since early reports suggest a dose-response effect. CALGB trial C9342 is evaluating paclitaxel dosages in 300 patients who will receive 175 mg/m$^2$, 210 mg/m$^2$, and 250 mg/m$^2$, all given over three hours, but results have not yet been reported. The NSABP plans a sequential CA-to-paclitaxel study as well as a preoperative or postoperative docetaxel trial following preoperative CA.

The delivery of effective doses is an important issue in therapy and may affect overall outcome. Arbitrary dose reduction may result in poorer outcomes, and retrospective analyses suggest that increasing dose intensity improves response rates in metastatic breast cancer and freedom from relapse in stage II patients. Despite these findings, issues regarding the role of high-dose therapy in both metastatic breast cancer and in treating patients with a high risk of recurrence remain unresolved. The number of women who have received bone marrow or peripheral blood stem cell transplants as treatment for breast cancer has risen significantly over the last five years. Approximately 2,000 patients with breast cancer are treated annually with high-dose regimens, according to a national Transplant Registry. Two national trials currently underway restrict entry to women with 10 or more positive nodes, and another protocol for women with four to nine nodes has just begun. A retrospective comparison between results from transplantation and chemotherapy suggests benefit from this high-dose approach but, to date, no data have been derived in a prospective, randomized fashion to clarify which, if any, breast cancer patients will benefit most from this procedure.

Various selection factors - such as age, performance status, organ function, exclusion criteria, and prior response to treatment - can influence outcomes and can lead to erroneous conclusions regarding the relative merits of two treatments when not compared prospectively. Even premenopausal women with good performance status and ER-positive first-recurrence stage IV disease survive an average of five years when treated with CAF and oophorectomy. Thus, a comparison of conventional adjuvant chemotherapy vs high-dose chemotherapy and autologous bone marrow or peripheral blood stem cell transplantation as adjuvant intensification therapy following conventional adjuvant chemotherapy, as in the national trial (INT0121), is justified. This complements an earlier trial (C9082) in which high-dose cyclophosphamide, platinum, 1,3-bis(2-Chloroethyl)-1-nitrosourea (BCNU), and autologous bone marrow transplantation is compared with standard doses of the same agents as consolidation to adjuvant CAF. A recent randomized trial of 90 South African patients compared bone marrow transplantation to "conventional" chemotherapy for metastatic disease and suggested a benefit from transplantation. The interpretation of the trial is clouded, however, by the small number of patients studied, the use of an atypical "standard" chemotherapy arm (cyclophosphamide, mitoxantrone, and vincristine), and the use of tamoxifen in responding patients. More confusion regarding the role of high-dose therapy in metastatic breast cancer resulted following an analysis of 423 patients that compared immediate vs delayed high-dose chemotherapy after conventional chemotherapy with doxorubicin, fluorouracil, and methotrexate. The results showed a benefit in disease-free survival with immediate high-dose therapy but, paradoxically, an overall survival benefit from delayed high-dose consolidation with combination alkylating agents and autologous cellular support.

Node-Negative Breast Cancer Patients

The routine use of adjuvant chemotherapy in all node-negative breast cancer patients remains controversial. Since it became known that a significant number of patients with node-negative breast chemotherapy has disease recurrence, several prospective, randomized trials were designed to evaluate adjuvant chemotherapy in node-negative breast cancer. The first, which was organized by the Eastern Cooperative Oncology Group (EST1180), studied CMF with prednisone (CMFP) for six cycles in patients whose primary tumor was either ER-negative or greater than 3 cm. The second trial was conducted by the NSABP for ER-negative patients using methotrexate and fluorouracil with leucovorin rescue. A third trial, the European peroperative adjuvant trial, using CMFP was reported by the Ludwig Breast Cancer Study Group. All three trials demonstrated improvement in disease-free survival after five years of follow-up. In the NSABP study, premenopausal and postmenopausal patients benefited. An improvement in survival was seen at five years in the subset of postmenopausal ER-negative women treated with CMFP, and an overall survival benefit was seen at eight years in those women treated with CMFP. An additional five to 10 years of follow-up will be required to evaluate fully the long-term impact of these trials. CMFP and nonalkylating-agent chemotherapy using only methotrexate and fluorouracil confer a benefit in disease-free survival only for node-negative, ER-negative premenopausal patients, whereas tamoxifen does the same and may provide a survival advantage for node-negative, ER-positive postmenopausal women.

Most would agree that women with poor prognostic features (eg, tumor size greater than 2 cm, high nuclear grade, tumor necrosis) are reasonable candidates for adjuvant chemotherapy. Those women expressing high levels of HER-2/neu might even require high-dose chemotherapy. However, those with more favorable prognostic features (eg, tumor size less than 1 cm, diploid tumors, an S-phase fraction less than 10%) probably would not benefit from adjuvant chemotherapy since their overall prognosis is excellent. Conversely, for ER-positive, node-negative premenopausal breast cancer patients, adjuvant tamoxifen may be as useful as chemotherapy if they have good prognostic factors. ER status is not a good discriminant in node-negative patients, however, since the difference in disease-free survival between ER-positive and ER-negative patients at 10 years is only approximately 5%. Primary tumor size may be the most important factor in both ER-positive and -negative women, as noted in NSABP B-13 and B-14 node-negative trials. Flow cytometry or image analysis for determining diploid or aneuploid pattern and proportion of S-phase fraction or molecular markers (eg, epidermal growth factor receptor, HER-2/neu oncogene expression, p53 tumor suppressor gene expression) may offer potential in the future for identifying high-risk node-negative patients who would benefit from adjuvant therapy, but presently their use remains promising at best. Progesterone receptor is most helpful in node-positive patients. Thus, unresolved issues about adjuvant therapy for node-negative women with invasive breast cancer range from the selection of low-risk women who will not benefit from any systemic postoperative treatment (as suggested by Rosner and Lane) to identification of node-negative patients with unfavorable prognostic features that indicate a higher risk of relapse, where more aggressive adjuvant chemotherapy might be indicated.

Hormonal Therapy Issues

Early results from a trial by the Novolin Adjuvant Trial Organization in early breast cancer suggested a benefit from postoperative tamoxifen irrespective of nodal, menopausal, or ER status. Subsequently, the Scottish Trial using five years of postoperative adjuvant tamoxifen suggested improved disease-free and overall survival response rates as high as 94%, including a complete response rate of 40%, but is associated with congestive heart failure in 24% of patients receiving more than 360 mg/m$^2$ of cumulative doxorubicin. The latter issue precludes wide acceptance of this dosage schedule in the adjuvant setting for most subsets of patients, but other similarly effective dosage schedules might not have this toxicity profile. Trials are being conducted that use different schedules, limit the total dose of doxorubicin, add a cardioprotectant such as dexrazoxane, and use different drugs such as cisplatin. Results of an Eastern Cooperative Oncology Group trial (EST1193) will soon be reported that involves 739 patients with metastatic breast cancer. This trial compares three regimens: (1) eight cycles of 60 mg/m$^2$ of doxorubicin, (2) eight cycles of 175 mg/m$^2$ of single-agent paclitaxel given over 24 hours, and (3) the combination of eight cycles of 50 mg/m$^2$ of doxorubicin plus 150 mg/m$^2$ of paclitaxel per 24 hours plus G-CSF on days 3 through 12 for hematopoietic support. The relative response rates, toxicities, and survival results are critical issues to be scrutinized in assessing the potential role of paclitaxel in earlier disease.
benefit in node-negative patients treated with tamoxifen. The NSABP B-14 trial in node-negative, ER-positive patients showed benefit in delaying treatment failure at five years in both premenopausal and postmenopausal patients. A meta-analysis by the Early Breast Cancer Trialsists' Collaborative Group of premenopausal and postmenopausal women with stage I or II carcinoma supports the benefit of tamoxifen at 20 mg daily for at least two years or perhaps longer. Recent evidence suggests that ER-negative women benefit little from tamoxifen. In addition, there is a decreased incidence of contralateral breast cancer and cardiovascular mortality in women treated with tamoxifen. Unresolved issues regarding hormonal therapy include treatment of node-negative patients, the duration of tamoxifen treatment, ovarian ablation, and chemoendocrine therapy.

Additional unresolved issues in node-negative patients are the use of tamoxifen alone in premenopausal women, the role of surgical or medical castration alone or in combination with tamoxifen or chemotherapy, and the use of doxorubicin-based adjuvant chemotherapy regimens alone or with tamoxifen. Clinical trials evaluating these issues are currently underway. One Intergroup trial (INT0142) in premenopausal, node-negative, receptor-positive patients with a tumor size no greater than 3 cm is comparing tamoxifen alone for five years to tamoxifen plus ovarian ablation with monthly goserelin acetate with respect to outcome, menopausal and sexual issues, and quality of life. While this trial is designed to answer important therapeutic and quality-of-life issues, accrual to date has been poor.

Tamoxifen Duration

The duration of tamoxifen therapy remains an unresolved issue since the drug is widely used. Data from the NSABP B-14 trial involving 2,644 node-negative women showed no benefit from an additional five years of treatment, after patients had taken tamoxifen for five years. Two cohorts of patients were studied -- those prospectively randomized to receive either five or 10 years of tamoxifen, and those registered and eligible by having taken five years of tamoxifen who were randomized to five additional years or observation. Based on the results noted, the Data Safety Monitoring Committee recommended discontinuing adjuvant tamoxifen after five years. After a National Cancer Institute Clinical Alert publicizing this recommendation, opinions have ranged from full support of this recommendation to suggestions that it is premature to stop tamoxifen after five years based on the data presently available. This recommendation has inherently been extended to node-positive patients without adequate data to indicate benefit, no benefit, or even harm. A recent trial suggested event-free and overall survival benefit in both node-negative and node-positive postmenopausal patients after six to eight years of follow-up who were treated with tamoxifen for five years compared with those treated for two years. Experimental work suggests that tamoxifen affects both cell proliferation and apoptosis and, with prolonged use (ie, greater than five years), resistance may develop or tamoxifen may actually stimulate tumor growth, but current clinical evidence suggesting a detrimental effect from prolonged tamoxifen is meager. An analysis of two Eastern Cooperative Oncology Group trials in node-positive women -- EST 5181 for premenopausal patients and EST 4181 for postmenopausal patients -- both with a median follow-up in excess of 10 years, show benefit in patients randomly allocated to tamoxifen for five or more years following initial treatment with chemotherapy plus tamoxifen for 12 months. Two present large-scale trials, the worldwide ATLAS (Adjuvant Tamoxifen Long Against Short) involving 20,000 women and the United Kingdom's aTTom trial randomizing breast cancer patients to discontinue or continue more tamoxifen, hope to provide sufficient power to answer definitively the question of optimal tamoxifen duration.

Ovarian Ablation

The role of ovarian ablation in premenopausal ER-positive patients needs clarification. Ovarian ablation in women under the age of 50 years produces a survival benefit comparable to that seen with adjuvant chemotherapy in premenopausal women, which raises the issue of the endocrine-related effects of chemotherapy vs cytotoxic effects as well as the possibility that both modalities might have additive effects. An additive effect of tamoxifen and cytotoxic chemotherapy in postmenopausal women has been postulated.

Combined Chemoendocrine Therapy

The use of combined chemoendocrine adjuvant therapy for breast cancer has been tested since the mid-1970s, but the optimal use of these modalities is still unresolved. Inconclusive and sometimes contradictory results have been noted in many reports of controlled trials using chemotherapy with concurrent or prolonged tamoxifen. The latest meta-analysis suggests a 12% benefit with combined treatment, but most individual node-positive trials have not reported an overall long-term survival advantage. The Eastern Cooperative Oncology Group has not seen improved overall survival with CMFP plus tamoxifen given concurrently for 12 months in either premenopausal or postmenopausal node-positive patients. The NSABP B-16 trial reported a survival benefit in node-positive patients using doxorubicin plus tamoxifen compared to tamoxifen alone but with follow-up of only 3.4 years. Two recent trials using epirubicin-based combinations plus tamoxifen suggest an advantage with combined chemoendocrine therapy but show no significant overall survival benefit after three and one half and six years of follow-up. No survival advantage was noted in a recent neoadjuvant trial of chemoendocrine therapy in operable breast cancer, despite a clinical response rate of 83% but a pathologic complete response rate of only 11%.

Management of the Elderly

Breast cancer in the elderly is a complex issue with unique features that extend beyond the individual characteristics of the cancer itself. Age alone impacts considerably on screening practices, diagnostic testing, and treatment patterns of many older cancer patients, including women with breast cancer. Compared with younger women, fewer older women have screening mammograms, have thorough diagnostic testing once a cancer is detected, or receive postoperative breast radiation following partial mastectomy. While conventional therapies are similarly effective for older women who are diagnosed with breast cancer, a number of unresolved issues remain, including surgical management of the axilla, the need for postoperative radiation following partial mastectomy, and the use of systemic chemotherapy and newer hormone therapies.

While mastectomy for the older woman presents few issues, use of a more conservative procedure is associated with a number of issues. Traditionally, postoperative radiation is mandated as an adjuvant component to optimize local tumor control in the remaining breast and surrounding tissues, unless disabling comorbidities preclude an expected survival of reasonable length. Results with conservative surgery and radiation are equivalent to more extensive surgery in patients with local disease, including the elderly. However, the need for axillary dissection and postoperative radiation in all older women is being questioned. The requirement for radiation therapy is being studied in a randomized trial in which all patients will receive tamoxifen following lumpectomy if they are 70 years of age or older and have a primary tumor no greater than 3 cm with clear surgical margins and clinically negative axillary and supraclavicular nodes. Thus, the surgical issue of eliminating axillary dissection in some older patients, and the need for postoperative radiation in all older women with operable breast cancer treated conservatively, remain unresolved questions for some physicians.

Systemic adjuvant therapy for elderly women with node-positive breast cancer is relatively straightforward since tamoxifen is clearly beneficial, reduces the number of contralateral breast cancers, and is well tolerated. Issues on the quality of life of older patients are not well characterized in formal clinical trials, but the extended symptom-free time afforded tamoxifen-treated patients allows high-quality life and independence. Tamoxifen is the systemic treatment of choice for any elderly woman with breast cancer. Toremifene has recently become available in the United States for adjuvant use as well. The use of purer antioestrogens such as droloxifene and raloxifene and aromatase inhibitors such as anastrozole, letrozole, and vorozole are being studied in metastatic disease and, if effective and tolerable, may have a place...
Chemotherapy for all older postmenopausal patients is controversial, despite the activity of CMF in older patients with metastatic disease. In such patients, CMF is equivalent but not superior to tamoxifen, provided that dose adjustments are made to accommodate the decline in renal function that accompanies aging. Chemotherapy represents another treatment option for the elderly who fail tamoxifen or other treatments. Additional agents that can be administered safely to the elderly are needed, as are clinical trials exploring biologic conjugates, inhibitors of angiogenesis, matrix metalloproteinase inhibitors, and other growth inhibitory compounds.

References


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