New Clinical Trends in the Adjuvant Therapy of Early Stage Breast Cancer

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Recent clinical trials of adjuvant therapy for early stage breast cancer support two general observations. First, overall survival is not impacted by the extent of surgery. Low rates of axillary relapse in patients treated with total mastectomy alone combined with the availability of systemic therapy as a substitute for surgical control of the axilla mean that patients can often be spared the morbidity of axillary node dissection. In problematic cases, newer diagnostic approaches, such as sentinel node biopsy, can help in making appropriate treatment decisions. Second, systemic therapy can reduce the clinical manifestations of disease. The incorporation of more sophisticated approaches to predicting outcomes, to varying timing and dose of treatment, and to developing new modalities of treatment, including immunotherapy, will contribute to a general strategy aimed at reducing the tumor to a harmless parasite. These observations support a paradigm shift in our definition of 'adjuvant'. Rather than referring to the use of systemic therapy after the patient's known disease has been surgically removed, adjuvant therapy would be re-defined to refer to local therapy used to eradicate any residual tumor remaining after systemic therapy has been completed.

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The word 'adjuvant' in breast cancer treatment has traditionally been used to refer to the utilization of systemic therapy after the patient's known disease has been removed (1). Given the continuing evolution of our understanding of the biology of breast cancer, a paradigm shift in our definition of 'adjuvant' may soon be appropriate. Under the new definition, local therapy would be defined as the adjuvant treatment used to eradicate any residual tumor that still imposes a significant risk to the patient after systemic therapy has been completed. This concept opens the door for new strategies of systemic therapy that would attempt to reduce the tumor to a harmless parasite, rather than following the usual oncologic tactic of 'seek and destroy'. The other ramification of this concept is that surgery could evolve into minimally invasive approaches to the primary tumor, such as percutaneous methods of cryosurgery (2), laser ablation (3), and stereotactic excision (4), or the use of thermal energy by magnetic resonance-guided focused ultrasound (5). Can this concept be justified? The progress that has been made in how we view cancer therapy has been built on observations from clinical trials. This review will focus on observations in early stage breast cancer and how these observations may define future research directions.

OBSERVATION 1: THE EXTENT OF SURGERY DOES NOT IMPACT SURVIVAL

Results of axillary node dissection

The first significant observation is that the extent of surgery for invasive breast cancer does not impact survival. Breast conservation surgery has been shown in six randomized clinical trials to provide equal survival rates compared with mastectomy (6–11). If removal of the entire breast is not necessary for survival, then a survival benefit from removal of regional lymph nodes is unlikely. In the National Surgical Adjuvant Breast and Bowel Project (NSABP) B-04 trial (12), no difference in survival outcome was detected between patients randomized to total mastectomy compared with radical mastectomy. (Some clinicians question this result, because one-third of the patients randomized to total mastectomy actually had some axillary lymph nodes removed, under the surgical philosophy of ensuring complete removal of all breast tissue, including the tail of Spence.) In patients receiving radical mastectomies, attempts to improve on the results by the inclusion of adjacent nodal basins, such as the internal mammary lymph nodes, either with surgery (extended radical mastectomy) or with irradiation, have been unsuccessful in prolonging survival (13–16). Finally, a

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recent meta-analysis by the Early Breast Cancer Trialists' Collaborative Group detected no apparent difference in mortality in eight trials comparing axillary surgical clearance to irradiation (17).

Incidence of axillary relapse with no treatment

Since the choice of systemic therapy is increasingly based on features of the primary tumor and not the histologic status of the axillary lymph nodes, the role of axillary node dissection may center on the issue of local control. Of those patients with operable breast cancers treated with total mastectomy alone (neither dissection nor irradiation of the axilla) in the NSABP B-04 study, 21% developed regional disease and required a delayed axillary node dissection; less than 2% presented with an inoperable axilla (18). Recent studies involving observation rather than dissection of the axilla have reported ranges of axillary relapse from less than 5% to 30%, depending upon the primary tumor size and the length of follow-up (19–22). In a series by the University of Toronto (23), the incidence of axillary relapse at 10 years in patients treated with lumpectomy alone without an axillary node dissection or adjuvant irradiation or systemic therapy was 9% in 32 patients with tumors less than 10 mm in size, 26% in 53 patients with tumors between 10 mm and 20 mm, and 33% in 18 patients with tumors larger than 20 mm.

Systemic therapy as a substitute for surgical control of the axilla

Whether modern-day systemic therapy can substitute for surgical control of the axilla is still unknown. Some investigators have demonstrated a decrease in locoregional recurrence after mastectomy with adjuvant chemotherapy as compared with mastectomy and radiotherapy alone (24). Data from the NSABP-B-14 study suggest that tamoxifen may also influence local control in patients undergoing breast conservation therapy (25). Martelli et al. (26) reported only a 4% axillary relapse rate with a follow-up time interval of 72 months in 321 elderly patients with operable breast cancer and clinically uninvolved axillary lymph nodes who underwent surgery without axillary node dissection and received adjuvant tamoxifen.

The addition of irradiation has been shown to decrease recurrence in the nondissected axilla to less that 3% (16, 27, 28), and to lower local relapse after breast conservation surgery by at least 50%. In patients at low risk for nodal metastases, the lower axilla can be irradiated through the tangential fields used to treat the breast, and this may be sufficient for local control of the nondissected clinically negative axilla. The goal is to spare the patient the morbidity of an axillary node dissection (lymphedema of the arm, sensory numbness, and potential limitation of arm motion and strength). Although surgeons have traditionally felt this morbidity to be of no substantial effect, quality of life studies from the patient's perspective indicate that 40–60% of patients experience long-term side-effects (29, 30). If staging information from the axillary node dissection becomes unnecessary and if local control of the axilla can be provided with systemic therapy and irradiation, this aspect of the risk-benefit ratio of systemic therapy and irradiation of the axilla should be considered regardless of whether there is a survival effect.

Lymphatic mapping and sentinel node biopsy

A possible interim alternative to performing an axillary node dissection is the recently described technique of lymphatic mapping and sentinel node biopsy. Several investigators have confirmed the accuracy of sentinel lymph node biopsy in patients with breast cancer. Giuliano et al. (31) reported their experience with 174 lymphatic mapping procedures for breast cancer in which sentinel lymph node biopsy was followed by formal axillary lymphadenectomy and histologic examination. The sentinel node could be identified in 114 out of 174 (66%) cases, and the status of the sentinel node accurately predicted the status of the nodal basin 96% of the time. In a recent second series of 107 consecutive patients (32), their ability to detect the sentinel node increased to 94%. Other investigators have used a combination of the blue dye and a technetium-labeled sulfur colloid with a hand-held intraoperative gamma-detection probe to find the sentinel node. Albertini et al. (33) reported a 92% success rate for identifying the sentinel node using both lymphatic mapping procedures in 62 patients with intact breast primary tumors. Using either technique for mapping (32, 33), the sentinel node was 100% predictive of the axillary status as verified by the concomitant axillary node dissection. If histologic staging of the axilla does not affect clinical decision-making regarding systemic therapy, the future use of sentinel node lymphatic mapping may be in those clinical situations in which the indications for systemic therapy are borderline, such as with small invasive tumors, or in which the proposed systemic therapy is associated with increased toxicity.

OBSERVATION 2: SYSTEMIC THERAPY MAY REDUCE THE CLINICAL MANIFESTATION OF DISEASE

Clinical goals of systemic therapy

The goal of both the patient and her treating physician is to achieve a normal lifespan for the patient with an optimal quality of life. Although clinical studies often use 5- or 10-year survival rates for outcomes' analysis, the real 'cure' is obtained if the patient remains free of disease during her lifetime. During this interval, however, the underlying genetic or molecular signs of occult residual cancer may persist (34). Thus, a clinical cure may not always require the eradication of all evidence of cancer cells but only the control of any of their deleterious effects (35).

Table 1

Percent decrease in the annual odds of breast cancer recurrence or death: The Early Breast Cancer Trialists' Collaborative Group meta-analysis of therapy results (36)

Therapy	Age (years)	Percent decrease	
		Recurrence	Death
Tamoxifen vs. none	<50	27 ± 07	NE[1]
	>50	30 ± 02	19 ± 03
Chemotherapy vs. none	<50	37 ± 05	27 ± 06
	>50	22 ± 04	14 ± 05
Chemotherapy + tamoxifen vs. chemotherapy	<50	NS[2]	NS
	>50	28 ± 03	20 ± 04
Chemotherapy + tamoxifen vs. tamoxifen	<50	NE	NE
	>50	26 ± 05	NS

[1] NE: Not evaluable
[2] NS: Not significant

Current systemic therapy (adjuvant chemotherapy and/or hormonal therapy) reduces the annual odds of recurrence and death (36) (Table 1). Whether this effect is due to the true elimination of micrometastatic disease or to prolongation of the time to relapse is unclear. The lack of a plateau effect in disease-free survival curves supports the latter contention (37). The relatively small but still significant survival effect is proportionally weighted by the risk of recurrence.

Determining guidelines for systemic therapy

Predictors. Current guidelines for the use of adjuvant systemic therapy are usually based on the age of the patient, the histologic status of the axilla, the size and histologic subtype of the primary tumor, and the level of estrogen receptor expressed by the tumor. However, numerous other prognostic factors may also correlate with survival: nuclear grade (38), lymphatic vessel invasion (39), indicators of tumor-proliferative activity (thymidine labeling index, flow cytometry, mitotic index, immunohistochemical detection of nuclear protein Ki67) (40–43), presence or absence of bcl-2 (44), and the expression of angiogenesis factor VIII (45, 46), plasminogen activator inhibitor-2 (47), and p53 (48, 49). Unfortunately, a reproducible model that uses combinations of these factors to accurately and consistently predict relapse rates has not been developed. The 1995 recommendations of the International Consensus Panel for clinical decision-making regarding adjuvant systemic therapy are shown in Table 2 (50).

Type of treatment regimen

No consensus has been reached regarding the most effective type of drug regimen. Although there is a growing bias in favor of doxorubicin-based combination chemotherapy, especially in the high risk node-positive patient, conclusive evidence of doxorubicin superiority over CMF-like regimens has yet to be established (51–56).

No survival benefit has yet been conclusively demonstrated for initiating chemotherapy prior to surgical intervention or immediately perioperatively in patients with operable breast cancer (57, 58). However, this failure to demonstrate a survival difference may be due to the lack of an effective cross-over regimen for tumors that are

Table 2

Adjuvant therapy recommendations of the 1995 International Consensus Panel (51)

Breast cancer classification[1]	Adjuvant therapy recommendations	
	Primary	Supplemental[2]
Node-negative		
T<1 cm, ER-positive, grade 1, age>35 years	None	Tamoxifen
T 1–2 cm, ER-positive, grade 1–2	Tamoxifen	Chemotherapy
T>2 cm and/or ER-negative and/or grades 2–3		
Premenopausal ER-positive	Chemotherapy	Tamoxifen
Premenopausal ER-negative	Chemotherapy	None
Postmenopausal ER-positive	Tamoxifen	Chemotherapy
Postmenopausal ER-negative	Chemotherapy	Tamoxifen
Node-positive		
Premenopausal ER-positive	Chemotherapy	Tamoxifen
	Ovarian ablation	Tamoxifen
Premenopausal ER-negative	Chemotherapy	None
Postmenopausal ER-positive	Tamoxifen	Chemotherapy
Postmenopausal ER-negative	Chemotherapy	Tamoxifen

[1] T: Tumor size; ER: Estrogen receptor
[2] Not in routine use

Table 3

Recent chemoendocrine clinical trials with significant disease-free survival benefit in postmenopausal estrogen receptor-positive breast cancer

Trial	Treatment regimen[1]	n	5-year DFS[2] (%)
IBCSG (53)			
	TAM × 5 years	239	57
	Early CMF × 3 and TAM × 5 years	231	69
	Delayed CMF × 3 and TAM × 5 years	238	64
	Early/delayed CMF and TAM × 5 years	225	70
NSABP (54)			
	TAM × 5 years	772	84
	Sequential MFL × 6 and TAM × 5 years	767	89
	CMF × 6 and TAM × 5 years	768	90
SWOG (55)			
	TAM × 5 years	361	72[3]
	CAF × 6 and TAM × 5 years	563	79[3]

[1] TAM: tamoxifen; C: cyclophosphamide; M: methotrexate; F: 5-fluorouracil; L: leucovorin; A: doxorubicin
[2] DFS: Disease free survival
[3] 4-year DFS rates

chemoresistant to the initial induction chemotherapy. An effective preoperative crossover regimen may increase the likelihood of achieving a complete histologic tumor response. A reduction of viable tumor burden to less than a cm^2 with sequential induction chemotherapy is more likely to affect survival than the clinical partial responses now obtained with standard chemotherapy regimens. A potential crossover induction regimen now being explored involves the use of taxanes such as paclitaxel and taxotere (59). Taxane chemotherapy has a high probability of obtaining tumor shrinkage even in patients with anthracycline-resistant tumors (60). Regardless of whether a survival advantage is detected with induction chemotherapy, this approach often provides enough tumor volume reduction to permit breast conservation surgery with an optimal cosmetic result (57, 61, 62).

Breast irradiation is usually delayed until the completion of all chemotherapy. Although the sequencing of radiotherapy and chemotherapy is still controversial, two randomized clinical trials did not demonstrate any difference in local failure rates in patients who had completed chemotherapy first (63).

Intense interest in evaluating the effect of drug schedule on outcome has produced mixed results (53, 54, 64, 65). A significant improvement in disease-free and overall survival with postoperative sequential chemotherapy was observed in the Milan trial which compared alternating CMF with doxorubicin versus doxorubicin followed by CMF (64). An ongoing expansion of this concept by Norton et al. (66, 67) involves the use of sequential higher dose (dose-intense), rapidly sequenced (dose-dense) chemotherapy. This calculated dose-intensity was initially described as the time over which the chemotherapeutic agent has been administered (mg/m^2/week) (68). The incorporation of promising new chemotherapy drugs, such as paclitaxel, taxotere, and navelbine into these drug schedules is now being pursued (69, 70).

For postmenopausal women with either node-negative or node-positive breast cancer, results from randomized studies evaluating the efficacy of chemotherapy in addition to tamoxifen indicate a disease-free survival benefit over that of tamoxifen alone (71–74) (Table 3). Longer follow-up will determine the true magnitude of a survival effect, as prior trials with longer duration of chemotherapy but often shorter exposure to tamoxifen did not find a significant survival difference for women whose tumors were estrogen receptor-positive (75–78).

Another area under investigation is the use of aromatase inhibitors in the adjuvant setting. Aromatase inhibitors are currently considered second-line hormonal therapy after tamoxifen failure in patients with estrogen receptor-positive metastatic disease, as these drugs may have a more favorable toxicity profile than other anti-estrogen therapies (79).

Duration of treatment

The optimal duration of systemic therapy is currently being debated. For chemotherapy, data from clinical trials indicate that fewer than three cycles is not advantageous and no additional benefit is likely after 12 cycles (36, 80–84). For tamoxifen, the meta-analysis (36) of five randomized clinical trials that compared the duration of 1–2 years of tamoxifen to that of 3–5 years showed that patients with a longer exposure to tamoxifen had a reduction in recurrence ($22 \pm 8\%$) but not a significant decrease in mortality ($7 \pm 11\%$). A recent analysis of the NSABP B-14 study indicated that 10 years of tamoxifen use offers no survival advantage over 5 years (85). Several trials are

still in progress to address the issue of tamoxifen duration comparing 2 years versus 5 years, 5 years versus 10 years, or 5 years versus indefinite therapy. Some oncologists advocate the use of prolonged tamoxifen for its potential value in decreasing the risk of contralateral breast cancer (86, 87), stabilizing bone mineral density (88), and decreasing coronary heart disease (89). However, tamoxifen may be associated with a significant loss of bone mineral density in premenopausal women in contrast to postmenopausal women (90). It has also been found to clearly increase the risk of endometrial cancer (91, 92). A March 1997 update of information in a subset of 303 women in the NSABP B-14 protocol described an increase of posterior subcapsular cataracts for women on tamoxifen for an average duration of 4.8 years (9.2%) or for an average duration of 7.8 years (9.3%) compared with that of the placebo group (2.5%).

High-dose chemotherapy

Improved survival rates in patients at high risk for recurrence (≥ 10 positive axillary lymph nodes or residual tumor present in 4 axillary lymph nodes after induction chemotherapy) are anticipated but not yet proven with very high-dose chemotherapy approaches (93–96). The results of single arm trials of high-dose chemotherapy may be partially due to selection of patients with better prognosis (97). The use of hematopoietic growth factors and circulating progenitor cells has facilitated the ability to deliver such therapy with less acute toxicity (98, 99). Whether long-term effects will include an increased rate of second malignancies is unknown, but preliminary data concerning the leukemogenic effect of adjuvant therapy are worrisome, especially with the addition of anthracyclines or irradiation (100–102). Extremely high-dose chemotherapy programs should be used in the context of well-designed protocols, with the patient aware of the risks and current data limitations. As reliable predictors of response to different treatment modalities become available, the ability to individualize the treatment choice based on molecular markers may obviate the need for global therapy that may only benefit the few. A potential tumor marker for the stratification of patients into high-dose chemotherapy strategies is the over-expression of HER-2-neu (103, 104). The recent interest in quality of life issues and our ability to measure patient outcomes (105, 106) will increasingly demand that oncologists focus their efforts not only on the tumor but also on the patient herself.

FUTURE DIRECTIONS

The meager increase in absolute survival achieved by the emphasis on increased tumor cell kill may provide the stimulus to look for ways to control tumor growth, with or without these current therapies. As we learn more about the signal pathways and receptors involved in the growth regulation of tumor cells, it will be possible to design antibodies capable of inhibiting tumor growth and augmenting the effects of chemotherapy (107–111). Gene therapy may allow the human multidrug resistance (MDR) gene to be transfected into human marrow progenitors to instill a preferential resistance to a chemotherapy drug such as paclitaxel (112). Although the BRCA1 gene is rarely mutated in sporadic breast cancer, levels of BRCA1 mRNA and its protein are decreased in both hereditary and sporadic disease. Results of a pilot trial with an ovarian cancer nude mouse model indicate that delivery of a nonmutated BRCA1 into the tumor via a retroviral vector can suppress tumor growth (113). Encouraging observations have also been reported for an ElB gene-attenuated adenovirus, ONYX-015, that targets p53 of tumors but not normal cells (114). This tumor-specific cytolysis appears to augment the efficacy of concomitant chemotherapy. Other therapeutic possibilities include inhibitors of angiogenesis (115–117) and matrix metalloproteinases (118), retinoid-induced differentiation (119), and vaccines directed against tumor antigens such as muc-1 (120).

Rapid progress in this translational research may require clinical investigators to consider other approaches than the standard model of phase I/II clinical trials in patients with advanced metastatic disease. The high tumor burden and often chemoresistant tumor clones in late stage breast cancer may obscure potentially effective strategies using new agents, especially immunobiologic therapies.

CONCLUSIONS

Advances in breast cancer treatment will require multidisciplinary support of translational research conducted in an expeditious manner. Surgeons must be prepared to adopt new techniques that will allow minimally invasive surgery for breast cancer. Clinical investigators will be challenged to explore new therapies of tumor growth control in an earlier spectrum of disease with a lower tumor burden. A more intense research focus in understanding the molecular genetics of breast cancer may provide the clues to primary prevention of the disease. World-wide public education will be essential for reducing mortality from breast cancer with earlier detection and for encouraging broad participation in ongoing and future clinical trials.

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