The Importance of Distant Metastasis and Its Impact on Survival Rates on Early-stage Hormone Receptor-positive Breast Cancer

a report by
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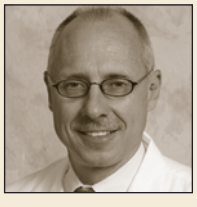
Breast cancer remains the second leading cause of cancer death in women in the US and it is estimated that 40,460 American women will die of the disease in 2007.[1] Moreover, recurrence has a significant impact on breast cancer mortality. Indeed, distant metastasis—the most common form of recurrence in the majority of cases[2–4]—represents the main cause of death in women with breast cancer.[5] In recent decades improvements in early detection and the recognized benefits of adjuvant systemic therapy in reducing risk of distant relapse has contributed to a steady decline in breast cancer mortality,[6,7] but despite these advances distant metastasis remains a challenge. Improvements in screening and imaging techniques have helped in the early detection of breast cancer and this, in turn, has resulted in a greater number of patients presenting with early-stage breast cancer. In patients with early disease, a multimodal approach to treatment is essential for improving survival. Breast cancer recurrence—particularly distant recurrence—in women with early-stage disease is associated with increased mortality.[8] Treatments that can address the risk of breast cancer recurrence, especially distant metastases, have the potential to remain disease-free and improve overall survival in women with early-stage breast cancer. Adjuvant systemic therapy has demonstrated its benefits in reducing the risk of occult micrometastatic infiltration and is now recommended clinical practice for patients with node-positive and high-risk, node-negative breast cancer.[9] The challenges associated with distant recurrence in early-stage breast cancer are discussed in this review, with a focus on adjuvant endocrine therapy.

Early Breast Cancer and Distant Metastases

Widespread screening coupled with advances in imaging technologies has resulted in earlier detection of breast cancer. Consequently, more than half of the women currently presenting with breast cancer in the US have an early-stage form of the disease.[10] Early-stage invasive breast cancer is defined as breast cancer that has not spread beyond the breast or the axillary lymph nodes, and includes ductal carcinoma *in situ*, stage I, stage IIA, stage IIB, and stage IIIA breast cancers (see *Table 1*).[9]



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Metastasis occurs when tumor cells detach from the primary tumor and migration of these cells through the circulation can lead to the development of distant micrometastatic disease. Over the last century two dominant paradigms of tumor pathogenesis have influenced the management of breast cancer.[11,12] The original hypothesis, developed by Halsted, proposed that breast cancer was a local disease and tumor dissemination occurred via regional nodes. Moreover, local recurrence was a determinant of distant disease; therefore, treatment should involve aggressive loco-regional control, such as a radical mastectomy with extensive lymph node dissection.[13,14] The 'Halstedian Paradigm' has been displaced by the 'systemic' view (Fisherian Paradigm), which developed from the observation that in many women with breast cancer aggressive local control did not prevent distant relapse. This led to the view that women with early-stage disease may already have distant micrometastatic disease at the time of diagnosis, which increases their risk of later developing overt distant metastases, irrespective of the extent of loco-regional treatment.[15,16] This view switched the emphasis from aggressive local control to the importance of effective systemic therapy. In recent years, the systemic hypothesis has also been questioned, leading to the proposal of a third hypothesis by Harris and Hellmen: the spectrum theory. This theory encompasses elements of Fisher and Halsted and was proposed because patterns of metastasis do not always conform strictly to either of the earlier models. According to the spectrum view, tumor cells spread via lymphatic vessels in early-stage breast cancer and via hematogenous routes in late-stage disease.[17,18] Thus, failure to achieve initial loco-regional control may allow the later migration of tumor cells to distant sites, with a deleterious effect on the patient's long-term survival.

Prognostic Factors

Unfortunately, risk of distant metastasis is not uniform and several factors are known to increase the risk of distant relapse. These factors include large tumor size, involvement of lymph nodes and vascular invasion, tumor type and grade, hormone receptor status, and human epidermal growth factor receptor-2 (HER-2/neu) status.[19,20] Indeed, Goldhirsch et al., on behalf of the St Gallen International Consensus Conference, defined the size of primary tumor invasive component, estrogen receptor (OR) and progesterone receptor (PR) expression, nodal status, and HER-2/neu expression as the major risk factors that will influence adjuvant systemic therapy decisions.[21] Recently, tests have become available that analyze the composition of a variety of genes and have the potential to help determine those patients at risk of earlier relapse. Oncotype Dx is in clinical use to help provide better estimation of the score for recurrence in patients with hormone receptor-positive, node-negative, early-stage disease.[22] In early breast cancer, nodal status is a significant prognostic indicator and the risk of distant metastasis has been directly related to the

number of axillary nodes involved.[23] However, even patients with node-negative disease are at risk of distant relapse.[24]

Outcome

Distant metastases represent the main cause of death in women with early-stage breast cancer[5] and outcome is related to the prognostic indicators. Axillary nodal involvement at diagnosis has been linked with outcome. The five-year survival for node-negative patients is 82.8% compared with only 28.4% for those with ≥13 positive nodes. Similarly, patients with tumors <1cm had a five-year overall survival (OS) of nearly 99% compared with 86% for patients with tumors of between 3 and 5cm.[23]

Current Status of Therapy

Multimodal therapy is the treatment of choice for early-stage breast cancer and involves surgery, radiotherapy, and adjuvant or neoadjuvant systemic therapy with chemotherapy and/or endocrine agents and trastuzumab for HER-2-positive breast cancer.[9,21] The aim of adjuvant therapy is to reduce the risk of recurrence following surgery. While it is now acknowledged that adjuvant chemotherapy and endocrine therapy can improve disease-free survival (DFS) and OS in women with early-stage disease, questions remain regarding the optimal role of the various options. A review of data from seven clinical trials of adjuvant therapy for early breast cancer conducted by the Eastern Co-operative Oncology Group revealed that the peak hazard of recurrence occurred within the first two years after surgery. Women with tumors >3cm and those who had more than four positive nodes were at the greatest risk of relapse. Between years two and five the risk of recurrence slowly declined. From years five to 12, the mean hazard of recurrence remained constant at over 4% per year. Of note, patients with hormone receptor-negative, highly proliferate disease had a higher risk of relapse in the first five years after diagnosis, then their relapse rate sharply declined. Moreover, from years five to 12, the risk was significantly less than in OR-positive disease.[25] The Early Breast Cancer Trialists' Collaborative Group (EBCTCG) identified that women with hormone receptor-positive breast cancer have approximately 50% of their initial recurrence risk after year five. Furthermore, the risk of recurrences, particularly distance metastasis, remained as late as 15 years after diagnosis.[26]

Adjuvant Chemotherapy

There have been numerous studies using single-agent and polychemotherapy adjuvant regimens in early-stage breast cancer. EBCTCG meta-analyses of many of these trials clearly demonstrate that adjuvant chemotherapy can reduce the risk of recurrence in women with early-stage breast cancer.[26,27] Before the introduction of the taxanes—a group of drugs—the two most commonly employed regimens for adjuvant polychemotherapy were cyclophosphamide/methotrexate/fluorouracil (CMF), and cyclophos-phamide/doxorubicin/fluorouracil (CAF). Data from the Milan CMF trial and its long-term follow-up of 19.4 years showed a reduction in distant metastases (74 versus 48%; p=0.004) with adjuvant CMF (in lymph node-positive disease). The study also demonstrated a 26% reduction in the relative risk of death in the CMF arm.[28,29] The armamentarium of chemotherapeutic agents available for the treatment of breast cancer has expanded greatly over the past few decades, including the use of anthracyclins and taxanes. An overview of some of the advances was recently published.[30]

Adjuvant Endocrine Therapy

Tamoxifen has been the gold standard of adjuvant endocrine therapy for women with hormone receptor-positive breast cancer for several decades. The most recent EBCTCG meta-analysis reported that five years of adjuvant therapy with tamoxifen significantly reduced recurrence (41%) and mortality (31%) in women with estrogen receptor-positive tumors. The hazard ratio of distant recurrence with tamoxifen was 0.64 (0.05; p<0.00001). The analysis showed the overall breast cancer recurrence risk to be approximately 3% per annum; 2% per annum in node-negative patients; and 4% per annum in node-positive patients during the study period.[23] However, the benefits conferred by tamoxifen were not extended beyond five years and some studies have even shown detrimental effects.[2] Furthermore, the EBCTCG meta-analysis reported that more than half of breast cancer recurrences and deaths occur after the completion of tamoxifen therapy, which suggests that tamoxifen may be less effective at preventing distant relapses than loco-regional recurrences. Thus, women who have remained disease-free after initial adjuvant tamoxifen therapy are still at substantial clinical risk for a late relapse event. These compelling data clearly illustrate that new therapies and treatment paradigms that address the risk of recurrence, in particular distant metastases, are needed. Third-generation aromatase inhibitors (AIs)—anastrozole, letrozole, and exemestane—have shown potential in this role, both as initial adjuvant therapy and in the extended adjuvant treatment setting.[31,32,33] However, AIs are not suitable for all groups of women with hormone receptor-positive breast cancer.

Table 1: Current Staging Guidelines for Early Breast Cancer

Stage 0	Tis	N0	M0
Stage I	T1*	N0	M0
Stage IIA	T0	N1	M0
	T1*	N1	M0
	T2	N0	M0
Stage IIB	T2	N1	M0
	T3	N0	M0
Stage IIIA	T0	N2	M0
	T1*	N2	M0
	T2	N2	M0
	T3	N1	M0
	T3	N2	M0

T0 = primary tumor cannot be assessed; Tis = carcinoma in situ; T1 = tumor 2cm or less in greatest dimension (includes microinvasion 0.1cm or less in greatest dimension, T1mic); T2 = tumor more than 2cm but not more than 5cm in greatest dimension; T3 = tumor more than 5cm in greatest dimension; M0 = no distant metastasis; N0 = no regional lymph node metastasis; N1 = metastasis to movable ipsilateral axillary lymph node(s); N2 = metastases in ipsilateral axillary lymph nodes fixed or matted, or in clinical apparent ipsilateral internal mammary nodes in the absence of clinically evident axillary lymph node metastasis.
Adapted from National Comprehensive Cancer Network (NCCN), Practice Guidelines in Oncology, Breast Cancer v.2. 2007, 2006.

Treatment of Early-stage Hormone Receptor-positive Breast Cancer in Pre-menopausal Women

Tamoxifen is still the treatment of choice for managing endocrine responsive breast cancer in the adjuvant setting in pre-menopausal women. In comparison, the use of AIs in pre-menopausal women is contraindicated. A comprehensive discussion of the role of ovarian ablation (OA) in pre-menopausal women with breast cancer is not within the scope of this review and an overview of advances in OA in this setting was recently published.[34] An EBCTCG meta-analysis of the impact of OA on breast cancer recurrence revealed that at 15-year follow-up, pre-menopausal women treated with OA had statistically significantly higher relapse-free survival and OS rates (45 versus 39% and 52.4 versus 46.1%, respectively) compared with women in the control group. Interestingly, trials of OA plus chemotherapy compared with chemotherapy alone have shown no additional benefit.[35] Recently the role of

luteinizing hormone-releasing hormone (LHRH) analogs has been investigated in pre-menopausal women with hormone receptor-positive breast cancer, and early data suggest that LHRH analogs may be as effective as surgical OA in the treatment of metastatic breast cancer.[36,37]

Treatment of Early-stage Hormone Receptor-positive Breast Cancer in Post-menopausal Women

The development of the third-generation AIs has added to the armory of agents for the management of hormone receptor-positive breast cancer. Three AIs—anastrozole, letrozole and exemestane—have been investigated in post-menopausal women and there is now considerable evidence that AIs are well tolerated and may offer benefits beyond those seen with tamoxifen in this group of women with early-stage hormone receptor-positive breast cancer. The Arimidex, Tamoxifen, Alone or in Combination (ATAC) trial investigated anastrozole, tamoxifen, or the two agents combined as adjuvant therapy in 9,366 post-menopausal women with localized breast cancer. The study showed that the anastrozole treatment provided significant improvement in DFS in the intent-to-treat (ITT) population (relative risk reduction of 13%). In women with hormone receptor-positive disease this benefit was 17%. However, no benefit was observed in a subset of patients with node-positive breast cancer. Anastrozole significantly prolonged the time to distant metastasis in the ITT population, but although there was a trend to improvement in the hormone receptor-positive patient population this was not significant. Moreover, no significant OS advantage was noted with anastrozole in the overall population (hazard ratio (HR) 0.97; p=0.7) or in the hormone receptor-positive population.[32]

The Arimidex-Nolvadex 95 (ARNO 95) and Austrian Breast and Colorectal Cancer Study Group 8 (ABCSG 8) trials investigated anastrozole in the sequential adjuvant setting. A combined analysis of these trials was carried out in 3,224 post-menopausal women with hormone-sensitive early breast cancer who were randomized to continue tamoxifen or to switch to anastrozole after completing two years of adjuvant tamoxifen therapy. It revealed that women switching to anastrozole showed a significant improvement in event-free survival and a significant decrease in risk of metastasis (40 and 39%, respectively) compared with those continuing tamoxifen, at a median follow-up of 28 months. However, OS was not significantly different between the groups.[38] Letrozole has also been studied in large phase III randomized, controlled trials in both the adjuvant and sequential adjuvant setting. In the Breast International Group 1-98 (BIG 1-98) trial, 8,028 post-menopausal women with endocrine-responsive breast cancer compared the effectiveness of tamoxifen or letrozole alone (five years), tamoxifen for two years followed by letrozole for three years, and letrozole for two years followed by tamoxifen three years.[39] The results from the primary core analysis of the trial data, which analyzed all events in the monotherapy, and the sequential arms up to the time of treatment switch (two years of therapy) with a median follow-up of 25.8 months revealed that letrozole monotherapy resulted in a significantly lower risk for recurrence with five-year DFS rate estimates of 84% compared with 81.4% for the tamoxifen group. Importantly, letrozole resulted in significantly fewer recurrences at distant sites (HR 0.73; 95% confidence interval (CI) 0.60–0.88; p=0.0012). At this short follow-up, OS did not differ significantly between the two groups. Data from the sequential arms, expected in 2008, are eagerly anticipated and will provide crucial comparative information on the benefit of sequencing letrozole and tamoxifen compared with frontline letrozole therapy, and help to clarify optimal treatment strategies. The MA.17 trial investigated whether extended adjuvant therapy with letrozole could effectively address the risk of late recurrence. The study was a randomized, double-blind, placebo-controlled trial conducted by the National Cancer Institute of Canada Clinical Trials Group (NCIC-CTG) and compared the effectiveness of extended adjuvant therapy with letrozole versus placebo in 5,187 post-menopausal women with primary breast cancer who had previously completed five years of adjuvant tamoxifen therapy. The first interim analysis of the trial revealed a significant DFS benefit of extended adjuvant letrozole therapy compared with placebo. Subsequently, the trial was unblinded early on the recommendation of the data monitoring and safety committee.[40] The final data analysis, at 30 months of follow-up, showed a significant 40% reduction in the risk of distant metastasis in the letrozole group compared with the placebo group (HR 0.60; 95% CI 0.43–0.84; p=0.002). Moreover, final estimated four-year DFS was significantly higher in women treated with letrozole than in those treated with placebo, and improvement in DFS was consistent across all types of events (loco-regional recurrence, distant metastasis, and contralateral breast cancer), irrespective of nodal status and prior chemotherapy. In the study, extended adjuvant letrozole significantly improved OS in patients with node-positive disease, who comprised approximately 46% of the study participants, compared with placebo. Notably, this survival advantage is the first to be demonstrated with AI use in women with early breast cancer.[41] Exemestane was investigated in the Intergroup Exemestane Study (IES), which randomized 4,742 post-menopausal women with early breast cancer who were disease-free after 2–3 years tamoxifen therapy to continue tamoxifen or switch to exemestane for completion of five years of adjuvant therapy.[31,42] At median follow-up of 55.7 months, a 17% improvement in time to distant recurrence in the ITT population (HR 0.83, 95% CI 0.7–0.98) and an 18% improvement in time to distant recurrence in the OR-positive or unknown population (HR 0.82, 95% CI 0.69–0.98) was found in favor of the exemestane-treated group. The study also revealed that exemestane treatment provided a significant 17% improvement in OS in OR-positive or unknown patients (HR 0.83; p= 0.05) compared with tamoxifen.[42]

Recurrences

Unfortunately, many women with hormone receptor-positive early breast cancer will experience a recurrence, and this can occur at any stage of disease, observation time, and after any treatment modality. An EBCTCG meta-analysis showed that the risk of recurrence risk was greatest in the first few years following initial diagnosis of early breast cancer for those patients not receiving adjuvant endocrine therapy.[43] Moreover, the risk of recurrence remains up to 15 years post-diagnosis.[26]

Pattern—Local versus Distant

The most common recurrence event in women with breast cancer is distant metastasis. This is due, in part, to improvements in surgical techniques and the greater adoption of radiotherapy following breast conservation surgery, which has resulted in a reduction in local recurrence risks.[44] Advances in imaging technology have also alleviated the problem of missing extensive or multifocal sites of cancer in the breast at the time of surgery.[45] A retrospective cohort study showed that median time to all-cause mortality is significantly longer in women with loco-regional recurrence than in those with distant metastasis (6.4 versus 3.4 years, respectively).[46] Moreover, 10-year survival in women with local recurrence was 56% compared with 9% in those with distant recurrence.[47]

Strategies to Improve Outcomes

Starting tamoxifen therapy with the intention of switching to an AI after 2.5 or five years could potentially forfeit the early benefits associated with AIs over tamoxifen.[48] Moreover, it must be noted that several studies have indicated

that all AIs may not be alike in terms of their efficacies. Indeed, a recent analysis of early recurrences (at 30 months) in the ATAC trial demonstrated that anastrozole greatly reduces the risk of early local recurrence, but not in the reduction of distant metastasis, which is the most common early relapse event and a surrogate for OS.[49,50] In contrast, recent data from the BIG 1-98 show that letrozole had a large impact on reducing early distant recurrences (30% fewer distant recurrences).[51] Furthermore, if, theoretically, an AI might partially inhibit the activation of dormant metastasis by the act of surgery, then an AI should be started at the time of (or even prior to) surgery to maximize this benefit.[52]

Conclusions

Recurrences from breast cancer after successful therapy still cause major morbidity and mortality in spite of the use of adjuvant treatment. More recently, it has become clear that replacing tamoxifen in initial adjuvant endocrine therapy with an AI can avoid a number of early recurrences in post-menopausal women. There is also increasing evidence that AIs can reduce the risk of distant recurrences. This is particularly important because these more often lead to death of the patient. With the early use of AIs, we are improving outcomes and, potentially, saving more lives. ■

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