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Clinical Outcome in Stage I to III Breast Carcinoma and eIF4E Overexpression

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Objective

The objective of this study is to determine if high eukaryotic initiation factor 4E (eIF4E) overexpression (sevenfold elevation or more over benign breast tissue) is associated with a worse clinical outcome.

Summary Background Data

Dysregulation of cellular functions by selective overexpression of specific proteins can lead to malignant transformation. The overexpression of eIF4E preferentially increases translation of mRNAs with long, G-C rich 5′-untranslated regions. Selective gene products, such as tumor neoangiogenic factors, ornithine decarboxylase, and cyclin D1, are upregulated.

Methods

One hundred fourteen breast specimens were analyzed and eIF4E overexpression was quantified by Western blot analysis. Quantification for eIF4E protein level was accomplished using a rabbit anti-eIF4E antibody and colorimetric development of Western blots using nitro blue tetrazolium and 5-bromo-4-chloro-3-indolyl phosphate. The blots were scanned and analyzed by densitometry. Treatment, pathologic, and clinical outcome data variables were analyzed. Statistical analysis was performed to determine if eIF4E overexpression is associated with breast cancer clinical outcome.

Results

In the 55 benign specimens, the mean eIF4E expression was 1.1 ± 0.4 fold (mean ± standard deviation). All 59 malignant breast carcinoma specimens were noted to have eIF4E overexpression (range, 1.9-fold to 30.6-fold), with a mean overexpression of 10.8 ± 6.3-fold. The mean level of eIF4E expression in malignant specimens was higher than benign specimens ($p < 0.05$, unpaired t test). The degree of eIF4E overexpression appears to be independent of T and N stage.

In the 21 patients with eIF4E overexpression of less than sevenfold, there was one cancer recurrence but no cancer-related deaths. In the 38 patients with high eIF4E overexpression (sevenfold or more), 14 patients had breast cancer recurrences ($p = 0.03$, log rank test), of whom 11 have died from the disease ($p = 0.04$, log rank test). The average follow-up interval in this study was 40 months.

Conclusions

Patients with stage I to III breast cancer and high eIF4E overexpression had a higher rate of cancer recurrence and a higher rate of cancer-related death when compared to similar-stage breast cancer patients with low eIF4E overexpression. Therefore, eIF4E protein overexpression may be of prognostic value in stage I to III breast carcinoma.

Malignant transformation is a multistep process involving errors in molecules critical for normal cellular functions. The dysregulation of protein synthesis has profound effects on normal cellular functions and may be a critical component of the process of malignant transformation. Thus, regulators of protein synthesis may be potential candidates as molecular markers for cancer progression.

Protein translation requires the unwinding of the 5′ untranslated regions (5′ UTRs) of mRNAs by the RNA helicase complex.[1,2] In general, mRNAs with long 5′ UTRs are less likely to be translated than are mRNAs with medium or short 5′ UTRs. The binding of initiation factor 4E (eIF4E) to mRNAs with long 5′ UTRs increases the likelihood of binding by the RNA helicase and subsequent translation

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Patient Compliance Is Critical for Equivalent Clinical Outcomes for Breast Cancer Treated by Breast-Conservation Therapy

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Objective

To determine the compliance with a standard breast-conservation therapy (BCT) program in a predominantly indigent, minority population of patients with early breast cancer (stage I and II) served by a rural state institution in the South; to compare the clinical outcomes of this group with those reported in clinical trials; and to examine the socioeconomic factors that may have contributed to the rate of compliance.

Summary Background Data

Disease-free survival and overall survival in early breast cancer treated by BCT versus modified radical mastectomy are reported to be equivalent in prospective randomized trials. However, patients enrolled in clinical trials may not be representative of patients living in the various diverse communities that make up the United States. The authors' hypothesis is that patients enrolled in clinical trials at the national level may not be representative of indigent patients in the rural South and that clinical trial results may not be directly applicable.

Methods

A retrospective review of 55 women with early-stage breast cancer treated from 1990 to 1995 was performed. Clinical data, compliance with treatment and clinical follow-up, and recurrence rates were examined. Statistical analysis performed include the Fisher exact test, Kaplan-Meier survival analysis, and log-rank test.

Results

Full compliance (defined as completion of the entire course of radiation therapy and clinical follow-up) with the BCT program was observed in only 36% of patients. Fifteen of the 35 noncompliant patients did not complete radiation therapy. A significantly higher local failure rate was observed: 8 of these 15 patients (53%) have had local failure. In contrast, patients who were either in full compliance with the BCT program or were deficient only in that they missed part of their clinical follow-up had local failure rates of 5% (1/20) and 10% (2/20), respectively. Age, race, stage of cancer, economic status (measured by availability of medical insurance), distance of patient's residence from the hospital, and education level were evaluated as potential predictors of compliance. None predicted patient compliance, although a trend toward higher compliance was noted in patients with a higher education level, as determined by literacy testing.

Conclusions

Compliance with the BCT protocol at the authors' institution was worse than reported in clinical trials, and noncompliance translated into a significant increase in the local failure rate. Factors examined suggest that literacy may play a role in predicting compliance. Although BCT should be discussed with all breast cancer patients, the judicious application of clinical trial data to an institution's local population is warranted.

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Several studies have reported that the percentage of patients with breast carcinoma treated by breast-conservation therapy (BCT) is lowest in the southern region of the United States.[1–4] Socioeconomic factors, such as age, race, income level, access to regional treatment centers, and education level, have also been proposed as determinants of the use of BCT for the treatment of early breast cancer.[5–7]

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Prospective Study of Eukaryotic Initiation Factor 4E Protein Elevation and Breast Cancer Outcome

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Objective

To validate the authors' initial hypothesis-generating observation that eukaryotic initiation factor 4E (eIF4E) protein elevation predicts a higher cancer recurrence rate in patients with stage 1 to 3 breast cancer.

Summary Background Data

Tumor size and nodal status continue to be the two most important independent prognostic markers in breast cancer, despite well-documented limitations. In a previous smaller retrospective study, eIF4E, important in the regulation of protein synthesis of mRNAs with long or complex 5' untranslated regions, appeared promising as an independent predictor of breast cancer recurrence.

Methods

Specimens and clinical data from 191 patients with stage 1 to 3 breast cancer were accrued prospectively. Data collected include stage of disease, tumor grade, age at diagnosis, and menopausal status. Endpoints measured were disease recurrence and cancer-related death. eIF4E protein level was quantified using Western blot analysis. Immunohistochemical staining was used to determine estrogen receptor, progesterone receptor, and HER-2/*neu* receptor status. Statistical analysis include Cox proportional hazards model, log-rank test, Kaplan-Meier survival curve, Fisher exact test, and *t* test.

Results

Patients were divided into three groups based on tertile distribution of eIF4E: low, defined as less than 7.5-fold elevation (n = 64); intermediate, defined as 7.5- to 14-fold elevation (n = 61); and high, defined as more than 14-fold elevation (n = 66). The relative risk for cancer recurrence with intermediate elevation was 4.1 times that of patients with low elevation. For patients with high elevation, the relative risk for recurrence was higher, at 7.2 times that of the low group. The relative risk for cancer-related death for high elevation was 7.3 times that of patients with low eIF4E. Using multivariate analysis, high eIF4E remained an independent predictor of cancer recurrence after adjusting for tumor size, tumor grade, nodal disease, estrogen receptor status, progesterone receptor status, and menopausal status.

Conclusions

High eIF4E is an independent predictor of cancer recurrence in patients with stage 1 to 3 breast cancer. The relative risk for cancer recurrence increases with eIF4E protein elevation. High eIF4E elevation is also associated with an increased relative risk for cancer-related death.

To date, the two most important independent prognostic markers in breast cancer continue to be tumor size and nodal status.[1,2] However, systemic failure can and does occur in patients with small, node-negative tumors.[3] Approximately two thirds of invasive breast carcinomas present without evidence of axillary lymph node involvement, but at least 25% of these carcinomas eventually recur.[1,3] Conversely, more than 30% of node-positive breast carcinomas do not develop recurrent disease.[1] These inherent deficiencies in the TNM staging system have necessitated the search for a prognostic marker in breast carcinoma, independent of tumor size and nodal status.

Malignant transformation is a multistep process, involv-

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A Prospective Trial on Initiation Factor 4E (eIF4E) Overexpression and Cancer Recurrence in Node-Positive Breast Cancer

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Objective: A previous study of patients with stage I to III breast cancer showed that those patients whose tumors were in the highest tertile of eIF4E overexpression experienced a higher risk for recurrence. This study was designed to determine whether high eIF4E overexpression predicts cancer recurrence independent of nodal status by specifically targeting patients with node-positive disease.

Methods: The prospective trial was designed to accrue 168 patients with node-positive breast cancer to detect a 2.5-fold increase in risk for recurrence. eIF4E level was quantified by Western blots as x-fold elevated compared with breast tissues from noncancer patients. End points measured were disease recurrence and cancer-related death. Statistical analyses performed include survival analysis by the Kaplan-Meier method, log-rank test, and Cox proportional hazard model.

Results: One hundred seventy-four patients with node-positive breast cancer were accrued. All patients fulfilled study inclusion and exclusion criteria, treatment protocol, and surveillance requirements, with a compliance rate >95%. The mean eIF4E elevation was 11.0 ± 7.0-fold (range, 1.4–34.3-fold). Based on previously published data, tertile distribution was as follow: 1) lowest tertile (<7.5-fold) = 67 patients, 2) intermediate tertile (7.5–14-fold) = 54 patients, and 3) highest tertile (>14-fold) = 53 patients. At a median follow up of 32 months, patients with the highest tertile had a statistically significant higher cancer recurrence rate (log-rank test, $P = 0.002$) and cancer-related death rate ($P = 0.036$) than the lowest group. Relative risk calculations demonstrated that high eIF4E patients had a 2.4-fold increase in relative risk increase for cancer recurrence (95% confidence interval, 1.2–4.1; $P = 0.01$).

Conclusions: In this prospective study designed to specifically address risk for recurrence in patients with node-positive breast cancer, the patients whose tumors were in the highest tertile of eIF4E overexpression had a 2.4-fold increase in relative risk for cancer recurrence. Therefore, eIF4E overexpression appears to be an independent predictor of a worse outcome in patients with breast cancer independent of nodal status.

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In women, breast cancer is the most common malignancy and is the second leading cause of cancer death.[1] Current American Joint Committee on Cancer (AJCC, 6th edition) staging of breast cancer is based on the TNM status (Tumor size, presence of Nodal disease, presence of Metastasis) at diagnosis.[2] At present, the single most important prognosticator for breast cancer outcome is the status of the axillary lymph nodes.[3,4] Unfortunately, even in patients with node-negative breast cancer, 20% will develop systemic disease.[3,5] Conversely, long follow up of node-positive patients demonstrated that up to 35% of patients do not develop systemic disease.[3] Thus, clinicians deciding on adjuvant therapy based on tumor size and nodal disease continue to long for more refined prognostic markers that can better stratify patients with breast cancer and their risk for cancer recurrence.

The evidence for the importance of translation control in malignant transformation and tumor progression is accumulating. Translation control refers to the regulatory control of mRNA translation into polypeptides. Important in this regulatory role are the initiation factors, one of which is eukaryotic initiation factor 4E, or eIF4E.[6]

eIF4E is a 25 Kilodalton (Kd) cap-binding protein. It recognizes the 7-methylguanosine cap in the 5′ untranslated regions (5′ UTRs) of mRNAs. By binding to the cap, eIF4E facilitates the attachment of the "RNA helicase complex," eIF4F.[7,8] Figure 1 illustrates the cap-binding protein eIF4E and its attachment to the mRNA cap at the start of the 5′ UTR. This facilitates eIF4F binding and the subsequent recruitment of ribosomes to initiate protein synthesis. The binding of eIF4F leads to the unwinding of the 5′ UTR and hence the reduction of steric hindrance associated with long 5′ UTRs. eIF4E is limited in quantity; thus, eIF4E binding is

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High eIF4E, VEGF, and Microvessel Density in Stage I to III Breast Cancer

[Original Articles]

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Abstract

Objective: In a prospective trial, to determine if eIF4E overexpression in breast cancer specimens is correlated with VEGF elevation, increased tumor microvessel density (MVD) counts, and a worse clinical outcome irrespective of nodal status.

Summary and Background Data: In vitro, the overexpression of eukaryotic initiation factor 4E (eIF4E) up-regulates the translation of mRNAs with long 5'-untranslated regions (5'-UTRs). One such gene product is the vascular endothelial growth factor (VEGF).

Methods: A total of 114 stage I to III breast cancer patients were prospectively accrued and followed with a standardized clinical surveillance protocol. Cancer specimens were quantified for eIF4E, VEGF, and MVD. Outcome endpoints were cancer recurrence and cancer-related death.

Results: eIF4E overexpression was found in all cancer specimens (mean ± SD, 12.5 ± 7.6-fold). Increasing eIF4E

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ADVANCES IN SURGERY

Adjuvant Therapy for Patients Who Have Node-Positive Breast Cancer

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Patients who have node-positive breast cancer are at risk of dying from recurrent disease [1]. The risk of recurrent disease has been significantly reduced by decades of meticulous and incremental discoveries at the bench-side, which were then translated to the bedside. With better understanding of the biology and natural history of breast cancer, novel therapies were developed, tested, and ultimately incorporated into the armamentarium against breast cancer, culminating in measurable positive outcomes for these patients.

In 1974, the estimated overall 5-year survival for patients who had breast cancer was 75%; in 2000, this figure approaches 90% [2]. This improvement shows that the investments made over the decades have resulted in a generous return. This article outlines the progression and evolution of adjuvant therapy for node-positive breast cancer, starting with single-agent chemotherapy, progressing to polychemotherapeutics, to taxane-based therapy, and, more recently, to target-specific biologic agents (trastuzumab). It also discusses the evolution of endocrine therapy, from tamoxifen to the aromatase inhibitors, and the role of postmastectomy radiation therapy (PMRT).

OUTCOME WITH SURGERY ALONE

Historic data from the 1970s demonstrated that recurrences in node-positive patients following a definitive operation (radical mastectomy) alone were

This article outlines the progression and evolution of adjuvant therapy for node-positive breast cancer, starting with single-agent chemotherapy, progressing to polychemotherapeutics, to taxane-based therapy, and, more recently, to target-specific biologic agents (trastuzumab). It also discusses the evolution of endocrine therapy, from tamoxifen to the aromatase inhibitors, and the role of postmastectomy radiation therapy.

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