Invited Review

The Role of Gene Signatures on Treatment Decisions in Early-Stage Breast Cancer

Erken Evre Meme Kanseri Tedavisinde Gen İmzalarının Rolü

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ABSTRACT

Breast cancer is a heterogenous disease with various morphological, clinical and molecular features. Traditionally, pathologic parameters and clinical stage of the disease are used to determine indication of adjuvant treatment, however these features are not sufficient to identify the patients that need treatment. Prognostic and predictive biomarkers are needed to develop personalized treatments. Predictive factors are indicators of response to a particular treatment. MammaPrint® (Agendia, Amsterdam, the Netherlands), Oncotype DX® (Genomic Health, Redwood City, CA), Prosigna® (Nanostring technologies, Seattle, WA) and Endopredict® (Myriad Genetics) are gene expression profiles that are used to predict the benefit of adjuvant chemotherapy and provide additional prognostic and/or predictive information. In this review, we discuss the role of gene expression signatures in treatment decision of patients with breast cancer.

Keywords: breast cancer, gene, recurrence score

ÖZET

Meme kanseri çeşitli morfolojik, klinik ve moleküler özelliklere sahip heterojen bir hastalıktır. Adjuvan tedavi endikasyonunu belirlemek için geleneksel olarak patolojik parametreler ve hastalığın klinik evresi kullanılır, ancak bu özellikler tedaviye ihtiyacı olan hastaları belirlemek için yeterli değildir. Kişiselleştirilmiş tedaviler geliştirmek için prognostik ve prediktif biyobelirteçlere ihtiyaç vardır. Prediktif faktörler, belirli bir tedaviye yanıtın göstergeleridir. MammaPrint® (Agendia, Amsterdam, Hollanda), Oncotype DX® (Genomic Health, Redwood City, CA), Prosigna® (Nanostring teknolojileri, Seattle, WA) ve Endopredict® (Myriad Genetics) adjuvan kemoterapinin yararı ve ek prognostik ve/veya prediktif bilgileri tahmin etmek için kullanılan gen ekspresyon profilleridir. Bu derlemede, meme kanserli hastaların tedavi kararında gen ekspresyon imzalarının rolünü güncel literatür ışığında tartışmayı hedefledik.

Anahtar Sözcükler: meme kanseri, gen, rekürrens skoru

Introduction

The widespread use of adjuvant systemic therapy in early stage breast cancer resulted in a reduction of up to 30% in 10-year mortality of breast cancer [1]. This benefit was shown to be independent of the patient's age, nodal status, grade and diameter of the tumor [1]. However, the different clinical course observed in the follow-up of patients with the same stage revealed the fact that breast cancer is a heterogeneous disease. Although the adjuvant treatment decisions are based on characteristics of tumor (hormone receptor, HER2 status, Ki67 proliferation marker, tumor size, grade and lymph node involvement) and patient (age and menopausal status), standard clinical and pathological features are insufficient to distinguish between patients who will benefit from the adjuvant therapy and those who will not [2]. Tools that were created to assist in decision making (Adjuvant! Online and PRECIT plus) do not consider biological

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characteristics of the tumor [3–6]. The patients treated with hormonal therapy alone, showed disease recurrence rates of less than 20% by 10 years after diagnosis, thus most patients with hormone receptor positive (HR(+)) lymph node negative disease would not benefit from the addition of chemotherapy [7]. Retrospective clinical studies show that 30-50% of patients with early-stage breast cancer receive unnecessary systemic therapy [1].

In the light of gene-expression profiling, several biological-based prognostic profiles are created using the expression of hundreds of genes. These tests, gene signatures, are developed to provide more precise cost-effective care, better prediction of clinical outcome and to determine the benefit of adjuvant chemotherapy, especially in hormone receptor positive lymph node negative patients since they are known to have low risk of recurrence [8]. With the introduction of gene signatures into practice, personalized treatment came up, that's aim is to protect the patient from overtreatment and toxic effects of chemotherapy. These advances in molecular technology change 30-40% of patients' systemic treatment decision [9]. Guidelines support the use of Oncotype Dx, Mamma Print, EndoPredict, Prosigna (PAM50) and Breast cancer index (BCI) as gene expression assays [10].

Herein, we aimed to evaluate the gene signatures and their aid to treatment decisions in early-stage breast cancer in the light of current literature.

Gene signatures

Recurrence Score

The recurrence score (RS) test (Oncotype DX) is a 21-gene expression profile that became available in 2004 [11]. It is a reverse-transcription polymerase chain reaction-based assay of 5 reference genes and 16 cancer-related genes which uses a continues scale from 1 to 100 to anticipate the 10-year disease recurrence risk and magnitude of adjuvant chemotherapy benefit in patients with early-stage HR(+), mostly lymph node negative but also 1-3 lymph node positive breast cancer [12]. Some of the genes are involved in cell proliferation and hormonal response which are associated with chemotherapy response [7].The RS is categorized into low (<18), intermediate (18–30), and high risk (≥31). The NSABP B-20 trial, one of the first studies seeking the relationship between RS and chemotherapy benefit, exhibited the cutoff points of RS when analyzed retrospectively [13]. The trial revealed that the addition of CMF (cyclophosphamide, methotrexate, 5-Fluorouracil) to tamoxifen reduced the risk of developing metastases in patients with RS greater than 31, but no benefit was seen in patients with lower RS (absolute decrease of recurrence at 10 years were 27.6% and 1.1%, respectively). Patients with RS 0-10 had outstanding outcomes with endocrine therapy alone. The chemotherapy regimen used in NSBAP B-20 trial was CMF or MF; however, in a small study conducted by Gianni et al.[14], it was shown that the relationship between RS and chemotherapy benefit is not regimen specific. Eighty-nine patients with locally advanced hormone receptor positive breast cancer were evaluated in the study and patients with RS<18 rarely had a pathological complete response (pCR) with neoadjuvant treatment consisting of anthracycline/taxane regimen. RS was shown to be positively correlated with the probability of pCR. Recently published studies investigating the impact of RS on neoadjuvant treatment decision showed Oncotype DX as a significant predictor variable of pCR where patients with a RS>25 are more likely to obtain a histological response type 0-1 [15,16]. In addition, in multivariate analysis, it was the most significant predictor in comparison to Ki67, estrogen receptor and initial tumor size. Multiple following studies demonstrated the benefit of 21-gene Oncotype

DX Breast RS in treatment decisions, which prevented overtreatment [17,18]. In a meta-analysis of four studies with more than 500 lymph node negative, HR(+) breast cancer patients, the chemotherapy recommendation rate was found to be decreased from 55% to 35% [19].

The uncertainty about the patients with a midrange score, RS 18-30, was evaluated in TAILORx study [17]. Endocrine therapy was found noninferior to the chemotherapy plus hormone replacement therapy in terms of invasive disease-free survival, local or distant recurrence and overall survival at 9 years (83.3% vs 84.3%, 94.5% vs 95.0% and 93.9% and 93.8%, respectively). Subgroup analysis showed minimal benefit of chemotherapy for patients 50 years of age and younger with RS of 16-25. The results were related to antiestrogenic effect gained by menopause induced by chemotherapy. NSABP B-20 and TAILORx trial together proved that Oncotype Dx can aid physician in chemotherapy treatment decisions, as node negative patients with RS 0-25 can safely receive hormone replacement therapy alone where patients with RS 26-100 derive benefit from chemotherapy followed by endocrine therapy. Accordingly, the National Comprehensive Cancer Network (NCCN) Guidelines prefer the use of Oncotype Dx as the only gene expression assay that predict chemotherapy benefit [20]. (Figure 1)

Although the journey of Oncotype DX started in lymph node negative patients, the usefulness of RS was evaluated in node positive breast cancer patients in the following time period. The SWOG-8814 trial was the first study aimed to evaluate the chemotherapy benefit in postmenopausal HR(+) Her2(-) patients with 1-3 lymph nodes [21]. The study concluded that N1 patients with RS 0-17 could be treated with endocrine therapy alone whereas patients with RS 31-100 achieved strong clinical benefit with anthracycline based chemotherapy. TransATAC study in addition to SWOG-8814 validated the use of Oncotype Dx in the node positive women and showed that the benefit gained with tamoxifen is also valid for anastrazole, with approximately 16% adjustment for the lower risk of disease recurrence with the aromatase inhibitor [22]. The first prospective data, WSG Plan B study, that report clinical outcome on node positive and negative HR(+) early breast cancer patients with RS<11 showed excellent 3-year-disease free survival rates (98%) with endocrine therapy alone [23]. The chemotherapy was omitted in the population, whose actually high risk by traditional parameters. Breast cancer specific mortality had been reported in the secondary analysis of the SEER registry where RS was strongly predictive of breast cancer specific mortality [24]. The subgroup analysis of SEER registry has additional importance in terms of evaluating the patients with tumors $\leqslant$ 5 mm in size, since gene expression profiles are not routinely recommended for T1a tumors. The risk was found elevated in this group with RS >31, even though the estimate lacks precision. The first analysis investigating both distant recurrence and breast cancer death rates were done by Stemmer et al. [18] in a large prospectively designed registry in patients with N1mi or 1-3 positive nodes. The distant recurrence rates and breast cancer death estimates for RS<18, 18-30 and >31 was 3.2%, 6.3%, and 16.9% and 0.5%, 3.4%, and 5.7%, respectively.

Although WSG Plan B study and SEER registry were accepted to be cornerstone of RS validation in node positive patients, recently published results of RxPONDER trial evaluating endocrine therapy alone vs. chemoendocrine therapy in patients with 1–3 positive nodes changed the practical impact of oncologists [25]. The RxPONDER cutoff level was 25 and those with RS of 18-25 received less chemotherapy compared to those with 26-30. The difference in chemotherapy recommendations was independent

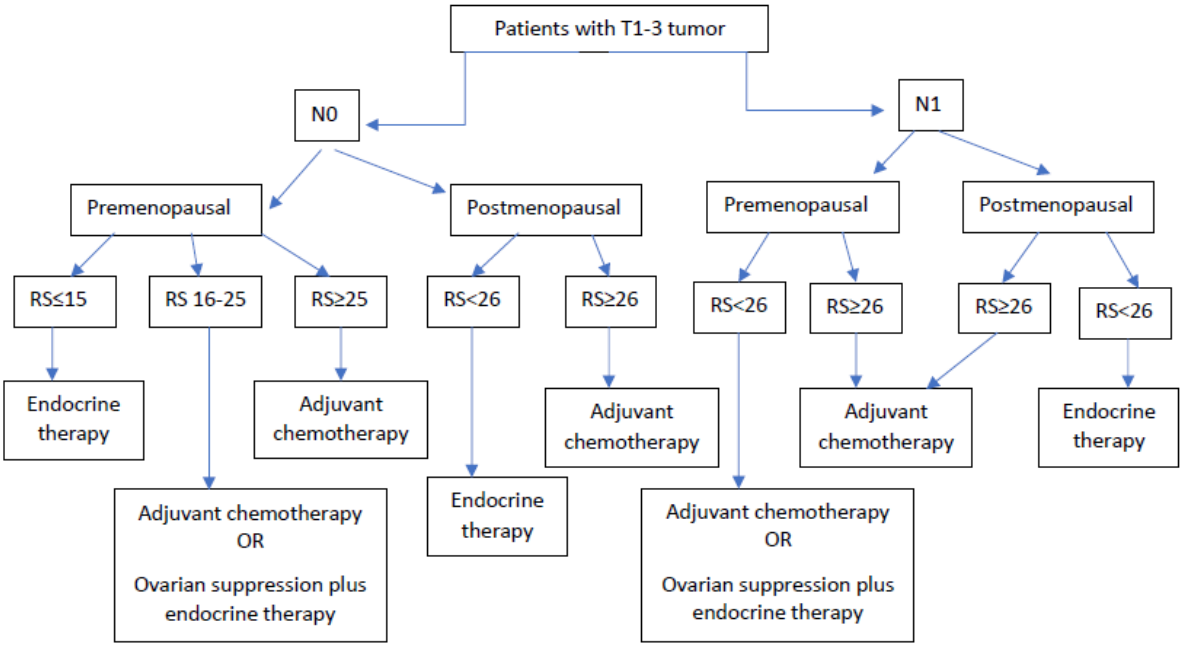

Figure 1: 21-gene (OncotypeDx) expression algorithm for Early-stage HR (+) Her2(-) Breast Cancer

from factors such as age, tumor size, and number of nodes involved. The results of the study changed the guidelines' in node positive patients [20].

MammaPrint

MammaPrint is a platform where 70 gene expressions are examined by microarray method. These genes are associated with cell cycle, invasion, metastasis, and angiogenesis. HR(+) positive patients are grouped as low or high risk. The practice changing done using MammaPrint assay is MINDACT trial, where prospective evidence for the addition of 70-gene signature to standard clinical-pathological criteria in selecting patients for adjuvant chemotherapy was provided [26]. The importance of the study was identifying a subset of patients who have a low risk of distant recurrence despite high clinical risk based on tumor size, grade and nodal status. Patients with low clinical and genomic risk received only endocrine therapy whereas ones with high clinical and genomic risk received chemotherapy. Patients with discordant results were randomized to chemotherapy and no-chemotherapy group. The 5-year survival rate without distant metastases were found 94.7% in high clinical/low genomic risk patients who didn't receive adjuvant chemotherapy. Among patients at low clinical and high genomic risk, 5-year survival with no distant metastases with and without chemotherapy were 95.8% vs 95.0%, respectively. As a result, using 70-gene signature for patients at high clinical risk is recommended to be able to omit chemotherapy. MammaPrint is also valuable in node positive patients as the rates of survival without distant metastases at 5 years were 96.3% vs 95.6% in patients who received and didn't receive chemotherapy, respectively. These data reveal that the benefit of adjuvant chemotherapy is small in patients with high clinical and low genomic risk [26]. In subgroup analyses, the benefit of chemotherapy was mostly seen in patients under <50y.

EndoPredict

EndoPredict (EP) is a 12-gene assay calculating a prognostic score using nine

cancer-related genes and 3 reference genes [27]. It is a platform used to predict distant metastasis in early-stage ER-positive, HER2-negative, lymph node-positive or negative patients. The EP clinical score (EPclin) is calculated using nodal involvement and tumor diameter [28]. Patients are classified as low (<3.3) and high (>3.3) risk. EP can predict both early and late recurrences. Based on the results of ABSCG-6 and 8 trials, patients with a low-risk score had risk of distant recurrence risk of 4% at 10 years [28]. On the other hand, node positive (1-3) patients with low score has a 5.6% risk of distant recurrence at 10 years [29]. In a study done by Müller et al. investigating the performance of EP in clinical practice, comparison of pre- and post-assay treatment decisions showed a change of therapy in 37.7% of patients [30]. 12.3% of patients had a change to an additional chemotherapy while 25.4% of patients changed to an endocrine therapy alone.

Prosigna (PAM50)

Prosigna (PAM50) studies the expression of 50 genes and 8 reference genes [31]. The risk of recurrence (ROR) score is calculated using 46 gene expressions, proliferation score, and tumor size. A score between 0-100 is given and patients are grouped as low (0-40), intermediate (41-60) and high risk (61-100). Risk of early (0-5 years) and late (5-10 years) distant recurrences can be predicted with this method in HR(+) Her2(-) lymph node positive or negative patients [29,32,33]. The prognostic value of PAM50 is well defined in a study done by Danish Breast Cancer Cooperative Group where patients with node negative disease has a distant recurrence risk of 5% after endocrine therapy if they have low ROR and 17.8% if they have high ROR [33]. The same study revealed the distant recurrence risk as <3.5% at 10 years with endocrine therapy alone in the patients with node positive disease. In TransATAC study, the similar group of patients didn't show ant distant recurrence at 10 years [29].

Brest Cancer Index

Breast Cancer Index (BCI) is created by combining two profiles: HOXB13/IL17BR (H/I) expression ratio and the molecular grade index (MGI). It can significantly determine the prognosis regardless of clinical factors (eg, age, tumor size, tumor grade and lymph node status) [34]. In ATAC trial, it was found prognostic in early-stage node negative patients for both early (0-5y) and late (5-10y) distant recurrence [22].BCI can identify patients who will benefit from endocrine therapy and who needs extended endocrine therapy.

Node-negative patients with T1 and T2 tumor and with BCI score between 0-5 (low) is placed into the same prognostic category as T1a-bN0M0, regardless of T score [35]. These tumors demonstrated a lower distant recurrence risk and extending endocrine therapy didn't show any significant improvement in terms of disease-free or overall survival. However, for patients with T1 tumor, BCI score of 5.1-10 (high) showed significant roles of distant recurrence in 5-10y period. Multiple trials investigating T1-3N0/+ HR(+) pre and postmenopausal patients with high BCI revealed significant improvement in disease-free survival with extended adjuvant endocrine therapy (5y of letrozole for postmenopausal and 10y of tamoxifen for premenopausal patients) [36–38].

Conclusion

Multiple studies with >96000 hormone receptor positive HER2(-) early breast cancer patients demonstrated the clinical benefit of Oncotype DX in personalized treatment. Since RS is also useful in determining the benefit from chemotherapy, it is superior to methods that detect similar gene expression profiles. Mamma Print, EndoPredict, Pam50 and BCI are other useful analyses that can be used to help estimate the recurrence risk. Head-to-head prospective comparison of the

assays is needed. Until then clinicians should order one of these assays in early-stage HR(+) HER2(-) breast cancer patients to omit chemotherapy and prevent its toxic effects, especially in patients who are candidates for endocrine therapy alone.

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