The role of VEGF in triple-negative breast cancer: where do we go from here?

Human breast cancers represent a heterogeneous group of tumors that are diverse in behavior, outcome and response to therapy [1]. The ‘traditional approach’ to the management of breast cancer has always involved the use of targeted therapies even before the targets were recognized. The use of endocrine therapy was initially based on clinical observation as this treatment evolved long before the identification of the estrogen receptor (ER). For trastuzumab, however, it was the recognition of the target that started the journey toward identification of appropriate targeted treatments. So, where does this leave those patients who have tumors that express neither hormone receptors nor HER-2?

It was the use of gene expression studies using DNA microarray analysis that resulted in the subclassification of breast cancers into five subtypes: luminal A and B, normal breast-like, basal-like and HER-2 positive [2]. Luminal A and B are derived from ER-positive tumors, while normal breast-like, basal-like and HER-2 positive are derived from ER-negative tumors. It was this subclassification that brought research to the forefront relating to the definition, manifestations and treatment of basal-like disease.

With respect to definitions, there has been considerable confusion in terminology between triple-negative breast cancers (TNBCs) defined as tumors lacking the expression of ERs, progesterone receptors, HER-2, and the basal-like type defined through gene array analysis. The two terms are frequently used interchangeably. TNBC represents 10%–17% of all breast cancers [3] and the majority (80%–90%) express a basal-like phenotype [1].

TNBC tends to occur in younger women and BRCA1 carriers. Clinically, they behave more aggressively, have a poor prognosis [4] and have an increased risk of distant recurrence (visceral and brain metastases) compared with women with non-TNBC tumors [1]. The only systemic therapy currently available is chemotherapy and the outcomes have been poor. Women with TNBC experience a higher risk of recurrence in the first 3–5 years after diagnosis with relatively few recurrences after 5 years compared with women with ER-positive disease [5].

Thus far, there are no specific systemic chemotherapy regimens recommended for women with TNBC but what is evident is that the metastatic disease course is frequently aggressive [6], with a median survival after the diagnosis of metastatic disease of 13 months [7]. These tumors may, however, be more sensitive to modern systemic chemotherapies (anthracyclines/taxane-based regimens) as seen in recent neoadjuvant studies in which women with TNBC have been observed to have high rates of pathological complete response [8]. Paradoxically, if they do not achieve a complete pathological response, these women tend to have a worse clinical outcome compared with those with non-TNBC [8]. There have been few prospective studies published to help guide clinicians in the systemic management of these patients. Studies to date have largely focused on DNA-damaging agents (cisplatin and carboplatin) based on the DNA repair dysfunction noted in BRCA1 carriers.

There is a clear need to identify biomarkers and more specific targeted therapies for TNBC. A number of biomarkers have been identified including structural proteins (basal cytokeratins 5, 15, 17 and vimentin), cell motility and adhesion-related molecules (P-cadherin and specific integrins), stem cell-related proteins (nestin and p63), potential or known tumor suppressors (p53), an inhibitor of apoptosis (alpha B-crystallin), angiogenesis mediators [e.g. vascular endothelial growth factor (VEGF)] and receptor tyrosine kinases (mesenchymal-epithelial transition and endothelial growth factor receptor) [9]. VEGF have been implicated as the major angiogenic factor in human cancers. VEGF promotes angiogenesis and invasion and increases vascular permeability. VEGF acts like a growth factor ligand that binds to tyrosine kinase receptors VEGFR-1 and VEGFR-2 on endothelial cells [10, 11]. High levels of VEGF expression have been associated with poor clinical outcome in many solid tumors [12]. Foekens et al. [12] found reduced survival times in patients with high levels of VEGF in the primary tumor, especially in large tumors and metastatic lesions. Similarly, Yamamoto et al. [10] found elevated serum and plasma VEGF levels in breast cancer patients with larger tumors and metastatic disease.

In this issue of *Annals of Oncology*, Linderholm and colleagues [13] explore the correlation of high expression of intratumoral VEGF levels with prognosis and overall survival (OS) in women with early-stage TNBC. This retrospective study examined 679 consecutive patients with primary operable invasive breast cancer, of whom 87 (13%) were classified as triple negative. The median level of intratumoral VEGF expression in the TNBC population was significantly higher (median 8.2 pg/μg, range 0–661.3) compared with the non-TNBC population (2.7 pg/μg DNA, range 0–502.1) and patients with TNBC had a significantly worse relapse free [hazard ratio (HR) = 1.8; \( P = 0.002 \); univariate analysis] and OS (HR = 1.8; \( P = 0.005 \)). Distant recurrences for TNBC were seen early with a peak from 1–4 years and a mean time from diagnosis to first recurrence of 18.8 months compared with 30.7 months in the non-TNBC group. The time between relapse and death was also shorter in TNBC (7.5 versus 17.5 months in non-TNBC; \( P = 0.087 \)) compared with the non-TNBC group.

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The results of this retrospective study are intriguing, although limited by the small numbers of patients with TNBC, the lack of grading in 20% of patients, the method for HER-2 determination (immunohistochemistry used in only 25% of samples) and the older systemic therapies delivered (i.e. combination chemotherapy with cyclophosphamide, methotrexate and fluorouracil). Although the median values for VEGF between the TNBC and the non-TNBC were significantly different, the ranges for both groups were large, implying heterogeneity within the groups. This study, however, is one of the first to report intratumoral VEGF level expression in the TNBC population. Clinical characteristics of the TNBC population described in this study are similar to those previously reported. The potential role of intratumoral VEGF expression levels in clinical practice remains unclear; however, VEGF has emerged as a potential therapeutic target in a number of solid malignancies, including breast cancer.

Clinical trials are now evaluating the potential benefit of VEGF inhibitors in the TNBC patient population. Previous studies using bevacizumab (a VEGF-specific blocking antibody) [5, 14] and sunitinib (a multikinase VEGF inhibitor) have been carried out in patients with metastatic breast cancer with no evidence of a specific benefit in TNBC disease that is not seen in the non-TNBC population. A large, international, randomized, open label, phase III trial is currently evaluating the efficacy and safety of adding 1 year of bevacizumab to standard adjuvant chemotherapy (anthracycline/taxane) in women with early-stage TNBC. The primary outcome is invasive disease-free survival and secondary outcomes are OS and toxic effects [15]. CALGB 40603 is an ongoing neoadjuvant trial for TNBC that will determine the benefit of adding either or both a platinum agent and an antiangiogenic agent to traditional chemotherapy in a 2 × 2 randomization schema [5].

Given the heterogeneity of breast cancer, including TNBC, it is unlikely that the identification of a single target such as VEGF and the subsequent development of a specific targeted therapy (e.g. anti-VEGF) will be adequate in the treatment of this disease. A number of other targeted therapies, given either as monotherapy or in combination with systemic chemotherapy, are currently being investigated in women with TNBC in the neoadjuvant and metastatic settings (clinicaltrials.gov).

Mammalian target of rapamycin (mTOR) is a central regulator of G1 cell cycle protein synthesis that precedes commitment to normal cellular replication. Inhibition of mTOR has been shown to have antiproliferative activity by deregulation of the phosphoinositide 3-kinase/Akt pathway in breast cancer [16–18]. A phase II study of the mTOR inhibitor, everolimus (RAD001), is being conducted in women with TNBC with a primary end point of time to progression [19].

Poly (ADP-ribose) polymerase (PARP) is a critical enzyme of cell proliferation and DNA repair, especially in the repair of tumor cells. PARP inhibitors effectively disarm the ability of cancer cells to repair themselves while sparing normal cells that lack cancer-related alterations, such as mutated BRCA1 and BRCA2 [20]. In cells that carry BRCA1 and BRCA2 mutations, one of the two major DNA repair methods, known as homologous recombination, is nonfunctional. The other major repair method, known as base excision repair, compensates for that loss. PARP-1 is up-regulated in the majority of patients with TNBC [21]. PARP-1 inhibition disables the base excision repair leading to cell death. The results of two phase II studies of PARP inhibitors in women with TNBC and BRCA-deficient metastatic breast cancer were presented at the 2009 American Society of Clinical Oncology Annual Meeting. At the plenary session, O’Shaughnessy et al. presented the results of a multicenter, open label, randomized phase II trial of gemicitabine/carboplatin alone or in combination with the PARP-1 inhibitor, BSI-201, in women with metastatic TNBC. The clinical benefit rate was significantly greater in the BSI-201 group compared with the chemotherapy alone group (62% versus 21%; P = 0.0002), and the addition of BSI-201 to chemotherapy led to an improvement in OS (9.2 versus 5.7 months; P = 0.0005) [22]. Similar promising results were seen with the oral PARP inhibitor, olaparib (AZD2281), which was investigated in a single-arm phase II study of BRCA1/2 mutation carriers with metastatic breast cancer [22]. A response rate of 41% and a median progression-free survival of 5.7 months were observed in those patients treated with olaparib 400 mg b.i.d. [23].

In summary, TNBC represents a challenging group of patients to treat, given the aggressive nature of the disease and poor prognosis. Heterogeneity has been demonstrated within this subtype of breast cancer making single therapeutic strategies unrealistic. The identification of ‘valid’ biomarkers and the subsequent development of strategic targeted therapies should form the basis of future trials in this patient population. VEGF represents an interesting target and a number of clinical trials are currently addressing the potential benefit of VEGF inhibitors in women with TNBC. The optimal therapeutic approach for these women has yet to be defined. Robust clinical trials to determine the ‘best’ chemotherapy for this subtype of breast cancer have yet to be conducted. Optimal treatment strategies for these women will likely include ‘TNBC-specific’ chemotherapy agents in combination with tailored targeted therapies.

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