Review

Triple negative breast cancer: heterogeneous disease

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Summary

Triple-negative breast cancer (TNBC) is a distinct subset of breast cancer defined by the lack of immunohistochemical expression of estrogen and progesterone receptors and epidermal growth factor receptor 2. It is a heterogeneous disease and displays overlapping characteristics with both basal-like and brca 1-2 BCs. This review evaluates the activity of emerging target agent in TNBC.

KEY WORDS: triple negative breast cancer, basal-like, heterogeneous disease, metastatic breast cancer.

Introduction

Breast cancer classification is in constant evolution, as advances in DNA and RNA microarrays as well as immunohistochemical (IHC) staining allow researchers to define the molecular heterogeneity of different disease subtypes and to guide the selection of appropriate treatment. Triple negative breast cancer (TNBC) is a clinical term characterized by the lack of expression of oestrogen receptor (ER), progesterone receptor (PR), and HER2 and expression cytokeratin CK5/6, and epidermal growth factor receptor (HER1). From an oncologist’s point of view, the great interest in TNBC is not surprising, given that previous studies have shown that these cancers benefit neither hormon al therapies nor from anti-HER2 therapies. The only systemic therapy currently available is chemotherapy. TNBC is a disease that account for approximately 12 to 17% of women with breast cancer and is known for its aggressive nature: development distant metastasis, shorter survival and high mortality rate (1-4).

Methods

This article provides an overview of relevant clinical and translational research finding in the field of TNBC, aiming to translate relevant findings in clinical practice. To ensure that TNBC sub-group analyses were identified, a bibliographic review of selected review articles was conducted. References for this review were identified by conducting searches of Medline and selecting references from relevant articles using the terms basal-like and triple negative and breast neoplasms.

Epidemiology

TNBC is associated with African-American or black ethnicity, menarche at an earlier age, younger age (under 40 years), advanced disease at diagnosis and premenopausal women. Other clinical association are obesity, metabolic syndrome but whether or not any of these clinical associations have a causal effect on developing TNBC has yet to be elucidated (5-7).

TNBC most commonly presented as a circumscribed mass without associated microcalcification and mammography may not be the ideal tool for early detection and thus RMN can play an important role in planning breast-conserving surgery.

A unique pattern of relapse has been observed amongst TNBC: in the first two years following diagnosis, there is a rapid rise in rate of relapse, with a peak within three years, followed by a rapid decline over the next five and a very low risk of subsequent recurrence (8).

After 10 years, relapse is more likely among patients ER-positive cancer than among patients ER-negative cancers. Significant of high proportion of distant recurrences, only rarely preceded by local recurrence. Thus, although as a group TNBC and basal-like cancers are biologically aggressive, many are potentially curable, reflecting their heterogeneity.

Data concerning lymph node metastasis are conflicting. Although some have reported higher prevalence of lymph node metastasis, others found no difference or even lower rate of of lymph node involvement.

Visceral relapse has been found to be more common than bone and lymph node metastases (Tab. 1). There is also a greater risk of brain metastases (10-16%). Because many studies did not find a relationship between an increase in tumor size and an increase in node positivity in TNBC it has been hypothesized that basal-like disease may have a hematogenous pattern of spread (9, 10).
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Using the transcriptome data set from 21 independent TNBCs (23-27).

The majority of TNBC are high grade ductal carcinoma and adenoid cystic carcinoma. However, caution should be used when stratifying risk among patients with TNBC with special histologic subtypes because tumor types such as classical defined medullary carcinoma and adenoid cystic carcinoma have an inherently favorable prognosis despite being classified as TNBCs (23-27).

Using the transcriptome data set from 21 independent breast cancer studies identified different clusters defined by mesenchymal features, immune system-related genes, DNA damage response genes, and activated androgen receptor signaling.

First cluster: claudin-low, characterized by the low expression of tight-junctions related genes (claudin 3, 4, 7) and high expression of mesenchymal and stem cell-like biological processes. The majority of claudin-low tumors were found to be either basal-like or normal-like by PAM50, and most showed a TNBC phenotype. In addition, claudin-low tumors were associated with metastatic and medullary histological differentiation and lymphocytic infiltration was found in 37% of cases. Since its identification, many groups have further characterized the claudin-low subtype in human tumors and preclinical models. However, its real frequency and clinical relevance are still under investigation (28-31).

Clinically the majority of claudin-low tumors are TNBC and from a biologically perspective the claudin-low subtype represents the most primitive tumors, on a scale of epithelial cell differentiation (32-34). The relationship between basal-like/TNBC and BRCA-1-related disease is also of great relevance.

The final TNBC cluster, importance of androgen signaling (38). The relationship between basal-like/TNBC and BRCA-1-related disease is also of great relevance.

To date gene expression profiling remains the gold standard to identify basal-like breast cancers but the complexity and costs limits its use in clinical practice. As the heterogeneity of TNBC is better defined, potential therapeutic targets are likely to emerge. A better understanding of the immune system is likely to foster new therapies designed to modulate immune response. For the time being, studies in TNBC are focused on evaluating the role of novel cytotoxics or available cytotoxic in combination with known target agents.

In summary TNBC show distinctive, but rather heterogeneous morphological, immunophenotypic and clinical features (39-41).

| Table 1 - Sites of first recurrence in TNBC vs non-TNBC. |
|-----------------|-----------------|-----------------|
|                | TNBC            | non-TNBC        |
| brain          | 30%             | 10%*            |
| lung           | 40%             | 20%             |
| liver          | 20%             | 30%             |
| bones          | 10%             | 40%             |

*higher in HER2 +++ pts

| Table 2 - Subclassification of TNBC (biomarkers, gene signature, BRCA disfunction). |
|-----------------|-----------------|-----------------|
| 1.              | BRCA1-mutant    |                 |
| 2.              | Immune system   |                 |
| 3.              | EGFR and cytoherins |               |
| 4.              | Different histologic subtypes | |
| 5.              | Claudin-low subtypes |            |
| 6.              | Basal-like tumors |                |

Diagnostic features

From a pathologist point of view, the interest in TNBC from overlapping features between basal-like and TNBC tumors. At the moment there is still no international consensus on the definition of these tumors. Perou et al. using a RNA expression arrays defined five molecular subtypes (luminal A and B, Her2 riche, normal breast-tissue like and basal-like). Basal-like breast cancer, which expresses genes usually found in the basal cells of normal breast, has since become an area of research interest (11, 12).

While TNBC is clearly defined by the absence of three marker expressions, there is no universally accepted profile of basal-like breast cancer (13). At the moment there is no universally accepted profile and what has become clear is that basal-like carcinoma and TNBC are neither exclusive nor synonymous disease because considerable discordance, approximately 25%, exists (14-18).

Some basal-like (18 to 40%) do not have a TNBC phenotype on immunohistochemical analysis and up to 20% of basal-like cancers express ER or overexpress HER2 (19).

TNBC disease is a heterogenous clinical entity composed of all the intrinsic molecular subtypes, with the basal-like-tumors predominating (Tab. 2). Previously described TNBC heterogeneity in part reflects tumor heterogeneity plus microenvironmental heterogeneity. Thus, TNBC disease is a broad and diverse category for which additional sub-classifications are needed.

TNBC and basal-like breast cancers share the same morphological features pushing border of invasion, stromal lymphocytic response, high nuclear grade, high mitotic count, high nuclear cytoplasmic ratio, apoptotic cell and poor differentiation, spindled tumor cells, squamous metaplasia, metaplastic features, geographical tumor necrosis, central sclerosis (20-22).

The majority of TNBC are high grade ductal carcinoma but less common specific type (metaplastic, medullary and adenoid cystic carcinomas). However, caution should be used when stratifying risk among patients with TNBC with special histologic subtypes because tumor types such as classical defined medullary carcinoma and adenoid cystic carcinoma have an inherently favorable prognosis despite being classified as TNBCs (23-27).
Treatment

Consideration for choosing loco-regional treatment for TNBC are the same as for other infiltrating ductal cancers and have demonstrated the extreme sensitivity to primary chemotherapy. Primary chemotherapy studies involving the administration of chemotherapy before surgery suggest that this treatment is very effective in the minority of women with TNBC cancer who have a complete pathological response and thus an excellent outcome; in contrast, the outcome for the majority who still have residual disease after treatment is relatively poor. These observations suggest that there is a sub-group of women with TNBC disease whose tumors are extremely sensitive to chemotherapy, but there are many women for whom chemotherapy is of uncertain benefit (42).

Since chemotherapy-resistant TNBC carriers a particularly poor prognosis, the identification of the mechanism of chemoresistance and therapeutic advance are critical. There is therefore a particular strong rationale for clinical research in this setting (43).

Liedtke reported that pCR rate is higher in TNBC compared with non-TNBC (22 vs 11%). Patients who achieved pCR had an excellent survival regardless of receptor status, but patients with TNBC and residual disease after primary chemotherapy have a significant shorter OS and postrecurrence survival than patients with nonTNBC and residual disease, particularly in the first 3 years (Tab. 3). This is likely due to two factors. First, TNBC in general has poor prognostic factors, including significantly higher nuclear grade, increase incidence of visceral metastases and shorter recurrence-free interval compared with non-TNBC. Second, chemotherapy is the only systemic treatment option for TNBC, whereas patients with non-TNBC may derive benefit from chemotherapy and endocrine therapy and trastuzumab as well. It is therefore not surprising that patients with non-TNBC and residual disease after primary chemotherapy who also received adjuvant endocrine therapy (if ER or PgR positive) showed better survival. TNBC may be best treated with third-generation regimens to be used in TNBC and their subgroups. There are no recommendation for specific treatment for TNBC who have DNA repair defects similar to BRCA-1 associated tumors; in this population, it has been demonstrated that anthracycline sensitivity and taxane-resistance may be predicted by a BRCA1 mutation but for patients with sporadically-occurring TNBC whose tumors have DNA repair defects, anthracyclines and taxanes remain the standard of care for TNBC patients with operable, node-positive breast cancer (48-50).

Relative anthracycline sensitivity and taxane-resistance among TNBC patients may hinge on BRCA1 function. The loss of BRCA-1 is associated with sensitivity to DNA-damaging chemotherapy as well as resistance to spindle poisons, such as taxanes and vinca alkaloids. This is relevant not only for carriers of the BRCA-1 mutation but for patients with sporadically-occurring TNBC whose tumors have DNA repair defects similar to BRCA-1 associated tumors; in this population, it has been demonstrated that anthracycline sensitivity and taxane-resistance may be predicted by a BRCA-1 associated expression signature. Colleoni showed that the classical CMF had a greater benefit in node-negative TNBC patients, suggesting may be a good choice for adjuvant therapy in certain populations (51).

Dose-dense and dose intensification has shown not only to improve PFS but also increase OS (52-55). There are no recommendation for specific treatment regimens to be used in TNBC and their subgroups. TNBC have a higher chemosensitivity compared with other breast cancer subtypes. However, they generally have a worse prognosis, mainly due to rapid progression in non-responders. So one of the important question is to find means to rapidly identify these non-responders, even prior to treatment. Eralp et al. found that anthracycline resistance is an important prognos-

**Table 3 - OS rate after primary chemotherapy in TNBC vs non-TNBC.**

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<thead>
<tr>
<th></th>
<th>TNBC</th>
<th>non-TNBC</th>
<th>p</th>
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<tbody>
<tr>
<td>pCR</td>
<td>22%</td>
<td>11%</td>
<td>0,03</td>
</tr>
<tr>
<td>pCR 3-year OS</td>
<td>94</td>
<td>98</td>
<td>0,24</td>
</tr>
<tr>
<td>non-pCR 3-year OS</td>
<td>68</td>
<td>88</td>
<td>0,001</td>
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EGFR overexpression is more common in TNBC and PgR negative (62) than in other subtypes (44 - 78%) and there may be an benefit with respect to PFS in women with ER negative breast cancer has resulted in at least as much of a inverse relationship between estrogen receptor expres-sion and survival (48). In advanced TNBC, responses to chemotherapy lack durability. In a retrospective series of 3,726 patients with 14.8 years of median follow-up, the median survival of patients with metastatic TNBC was only 6 months (57).

The most interesting clinical target in TNBC is the enzyme polyadenosine diphosphate-ribose polymerase (PARP) which is involved in base-excision repair after DNA damage. PARP inhibitors have recently shown very encouraging clinical activity in early trial of tumors arising in BRCA mutation carriers and in sporadic TNBC. Iniparib, in a phase II study in combination with gemcitabine and carboplatin demonstrated an improvement in tumor regression (48.9 vs 16%, p=0.002) in median PFS (6.9 vs 3.3 months, p<0.001) and median OS (9.2 vs 5.7 years, p<0.001) with a favourable safety profile in patients with metastatic TNBC (58-60).

The results obtained with PARP inhibitors so far repre-sent a real milestone in managing patients with BRCA-associated TNBC. However, there is still a critical need to identify patients without BRCA mutations likely to ben-fit from PARP inhibitors. In addition, more information about differences among PARP inhibitors and clarification of the exact mechanism of action of iniparib are needed. In vitro findings have shown that when a BRCA1-defective BC cell line was treated with veliparib, olaparib, or iniparib, DSBs increased in a dose-and time-dependent fashion. However, only veliparib and olaparib were able to inhibit PARP1/2. In contrast, iniparib was able to suppress genes involved in telomere function, which the authors suggest may be a result of blockade of other PARP family members (61).

Whether all TNBC patients will benefit from PARP-inhibitors or if only a portion of TNBC patients, such as BRCA-deficient tumors, will have clinical improvement beyond chemotherapy alone remains to be seen. The clinical utility of PARP inhibitors may become better real-ized if predictive biomarkers can be identified. Some TNBC and basal-like cancers may harbor a dis-functional BRCA1 pathway and thus may be sensitive to agents such as platinum salts. The role of platinum in non-BRCA-1 mutant advanced TNBC requires further validation.

The addition of the angiogenesis inhibitor bevacizum-ab to paclitaxel as first-line treatment for metastatic breast cancer has resulted in at least as much of a benefit with respect to PFS in women with ER negative and PgR negative (62).

Overexpression of EGFR is more common in TNBC than in other subtypes (44 -78%) and there may be an inverse relationship between estrogen receptor expres-sion and EGFR amplification, and use of the monoclonal antibody cetuximab, targeted against EGFR, is being further studied in combination with carboplatin. However, TNBC and basal-like cancer often display abnormal-

Conclusion

TNBC is a challenging disease that has lacked a standardized treatment approach both in the early and advanced setting. Available evidence suggests that among patients with TNBC, prognosis seems to vary according to factors such as age and pathological sub-type (66).

It seems very likely that neither TNBC nor basal-like are single entities but rather are a collection of different disease. The tumor biology of TNBC, basal-like breast cancer, BRCA-mutated machinery and claudin-low disease is both specific and diverse. A diagnosis of TNBC has currently important implications for choice of systemic therapies. It would be more clinically relevant to identify those patients whose TNBC are sensitive to specific chemotherapy agents (or combination thereof) and targeted therapies.

Emerging therapies aimed at damaging DNA, angiogenic players, tubulin structures, m-TOR, IGF-1R, AR, and HSP90 show promise in early stage studies, but their clinical performance has yet to be definitively proven (67-69).

Further research is needed to validate these new treatment options, alone or in combination with
chemotherapy. Given the fact that TNBC is such heterogeneous entity, another important research field is the validation of immunohistochemical markers, enabling us to better define subgroups with different clinical behaviours, and with predictive value towards sensitivity to chemotherapy and newer targeted treatments.

References


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