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Triple-Negative Breast Cancer: a brief overview.

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Triple-Negative Breast Cancer: a brief overview.

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Abstract

Background

Triple-negative breast cancer (TNBC) is a heterogeneous disease that accounts for 15-20% of all breast cancers. This represents the most challenging molecular subtype of breast cancer.

Methods

This article will make a comprehensive review of these therapies in the treatment of TNBC and it will give a glimpse into the near future of this difficult disease.

Results

Currently, chemotherapy is the standard treatment but active research tries to find actionable targets or other molecules to treat this aggressive disease with higher levels of success.

Immunotherapy has emerged as an attractive therapy in various cancers including this disease but other agents deserve our attention as well. Among these agents, the poly-ADP-ribose polymerase (PARP) inhibitors, platinum-based drugs, anti-epidermal growth factor receptor (EGFR) inhibitors, and anti-vascular endothelial growth factor receptor (VEGF) inhibitors are the most relevant ones.

Conclusion

Current treatment options for these patients are restricted to chemotherapy. However, research continues to advance and hopefully soon, other agents could be approved and use as standard approaches to this difficult disease.Â

Introduction

Triple negative breast cancer (TNBC) is a heterogeneous group of breast neoplasias, characterised by the lack of expression of oestrogen receptor (ER), progesterone receptor (PR), and the lack of overexpression or amplification of human epidermal growth factor 2 (HER2).

TNBC accounts for approximately 15â€“20% of all new breast cancers[1].

The incidence is higher in African-American women, young and patients with a germline BRCA1 mutation[2].

However, some data suggest that Hispanic women have a higher frequence of TNBC[3].

It is generally diagnosed at a more advanced stage when compared to other breast cancers and shows higher grade, BRCA1 mutations and usually family breast cancer[4].

It usually entails poor prognosis, shorter overall survival (OS) and earlier recurrences compared with oestrogen positive cancers[5].

The highes risk of recurrence remains within 3 years after the diagnosis, and the mortality is higher at 5 years[4]. Â

In fact, TNBC disseminates to distant organs with a higher incidence than its counterparts[6], although this incidence reduced with long-term follow-up becoming similar to non-TNBC[7].

Future for prevention of these breast cancers is poor. Premenopausal status, high BMA, use of oral contraceptives, although blamed as potential risk factors, their role in the incidence of TNBC is different according to several studies[4].

Until recently and due to its molecular characteristics, there have not been approved targeted therapies and standard treatment has remained cytotoxic chemotherapy.

The rate of responses to chemotherapy in early stages is high but unfortunately the risk for recurrence is also high and the prognosis remains shorter than for other types of breast cancer[1].

One issue to define TNBC is linked to a potential confusion at the time of defining clearly ER and PR status. In fact, IHC cutoffs (< 1% or < 10%) are used to show ER and PR features[8,9].

Recent protocols suggest a threshold â‰¥1% of immunoreactive cells[10].

Moreover, differences between HER2 positivity by IHC or by fluorescence in situ hybridization (FISH) have been reported[9,11].

The American Society of Clinical Oncology (ASCO) and the College of American Pathologist (CAP) have published guidelines to generalise these criteria.

HER2 is considered positive by IHC if >10% (3+) of protein expression in tumour cells. FISH determines the HER2 status by the ratio of the copy number over the number of assessed nuclei in 20 cells minimum.

Clear suggestions on tissue fixation and selection of antibodies have also been issued to avoid variability[12]. Â

Another area of confusion is with the BRCA1 germline mutation as most of them are triple negative withÂ a basal-like phenotype; however, the clinical approach could be different from the non-BRCA1 mutant TNBC.

Subtyping and molecular characteristics

Breast cancer has been divided into five molecular subtypes by gene expression profiling. Â The basal-like cancer showing expression of cytokeratines and EGFR, lack of ER, PR, and HER2 has got an aggressive behaviour[13].Â Â

It overlaps with TNBC although 25% of TNBC are not basal-like by gene expression, and some non-TNBC are basal-like by molecular profiling[14].Â

To simplify as much as possible the heterogeneity of TNBC, it has been subdivided into six subtypes based on molecular profiles[15].Â Â

Basal-like 1 (BL1), basal-like 2 (BL2), immunomodulatory (IM), mesenchymal (M), mesenchymal stem-like (MSL), and luminal androgen receptor (LAR) [15].Â Â

All differ in sensitivity to therapeutic drugs. BL1 responds mainly to platinum drugs. M is sensitive to phosphatidylinositol 3- kinase (PI3K) pathway blockers. LAR is more sensitive to androgen receptor inhibitors and it shows some resistance to standard chemotherapy[16,17].Â Â

This heterogeneity is in part responsible for the delay in developing new therapies against TNBC. The lack of actionable oncogenic mutations has also contributed.

There are some frequent genomic mutation is detected in TP53. This mutation or loss is present in 68% of TNBC and 80% of BL cancers. Unfortunately there is not a target therapeutic drug[18].Â Â Â

Some sporadic tumours have similar features to those that have a germline mutation in the DNA repair gene *BRCA1.*

The term â€˜BRCAnessâ€™ refers to genotypes of TNBC *BRCA* proficient but show similar clinical and biologic characteristics to *BRCA* deficient.

This phenotype will have relevant consequences as TNBCs that show failures in homologous recombination as will show treatment sensitivities as *BRCA* mutations[19].Â Â Â

Clinical course and prognosis

The central component of the therapy for TNBC is not unique but it is still the cytotoxic chemotherapy[20].Â Â Â Â

All patients with tumours > 0.5 cm must receive chemotherapy, neoadjuvant or adjuvant, as no clear evidence to use one over the other in terms of final results. However, the neoadjuvant strategies will offer measurable disease to assess response and provide prognostic information. This is also the preferred option for cases not operable or not eligible for breast conserving treatment due to tumour size or location.

TNBC shows higher responses to neoadjuvant chemotherapy compared to ER positive breast cancers and similar response rate to HER2 positive.

As expected, if pathologic complete response (pCR) is achieved, prognosis is improved[20].Â Â Â Â

In the neoadjuvant CALGB 40603 study, the addition of carboplatin or bevacizumab to neoadjuvant chemotherapy increased pCR rates. However, it remains unknown whether this will improve recurrence-free or OS[21].Â Â Â Â Â

However, despite that TNBC have got a higher rate of pCR than luminal breast cancers, will show higher recurrence rate.

This happens as a consequence of the worse prognosis it residual disease is present, which in TNBC seems to confer a shorter prognosis than in non-TNBC[21].Â Â Â Â Â

Regimens of systemic treatment

As for other types of breast cancer, the usually chosen regimens in neoadjuvant or adjuvant areas will count on anthracyclines and/or taxanes.

Adjuvant anthracyclines have shown a prolongation in disease-free and OS in comparison to regimens without anthracyclines.

HER2 has been shown to be a marker of anthracycline responsiveness, although the results are inconsistent. Gennary *et al* carried out a pooled analysis of the interaction HER2 status-efficacy of adjuvant anthracyclines and could not find any further benefit in survival parameters, either DFS or OS in cases with HER2 negative[22].Â Â Â Â Â Â

However, the optimal regimen is not clear yet and therefore, the final choice will depend on Â patientâ€™s characteristics and preferences.

A phase III trial carried out in 2006 compared the role of adjuvant A and cyclophosphamide (AC) to docetaxel/cyclophosphamide (TC) in all kinds of breast neoplasias. The disease-free survival (DFS) for TC was improved and this has led to consider this treatment as an effective non-anthracycline regimen[23] .Â Â Â Â Â Â

The efficacy of TC compared to AC plus a taxane (TaxAC) is not known. 2,125 patients were randomised to TC6 and 2,117 to have TaxAC. HR for TC6 versus (vs) TaxAC was 1.202 (95% CI, 0.97 to 1.49). At 4-years, the invasive disease free survival (DFS)Â was 88.2% for TC6 vs Â 90.7% for TaxAC (*P* Â = .04). Authors concluded that TaxAC regimens prolonged invasive DFS in high-risk HER2 negative compared with the TC6 regimen[24].Â Â Â Â Â Â Â

With all these data, we can conclude that anthracyclines should not be avoided unless other risks are present and TC should not be considered as an equal regimen in TNBC patients.

Additional cytotoxic agents

Antimetabolites are other group of antineoplastic drugs whose role in TNBC is not clear.

The FinXX study showed that adjuvant capecitabine combined with T, epirubicin, and C did not show any improvement in DFS or OS compared to standard regimens. However, TNBC had favourable survival outcomes when treated with the capecitabine-containing regimen in an exploratory subgroup analysis, although these results should be interpreted carefully due to the small sample[25].Â Â Â Â Â Â Â

NSABP B-38 trial assessed whether the addition of gemcitabine could improve results in comparison to two standard treatments. 4,894 patients, all with early-breast cancer node positive disease, were randomised to six cycles of T, A, and C (TAC), four cycles of dose-dense (DD) AC Â followed by four cycles of DD paclitaxel or DD ACâ†'P with four cycles of gemcitabine (G) incorporated to the DD paclitaxel. Authors concluded that gemcitabine did not add benefits and no significant differences were found in efficacy between DD ACâ†'P and TAC[26].Â Â Â Â Â Â Â Â

The CREATE-X study showed that adjuvant capecitabine monotherapy improved DFS and OS in HER2 negative if not pCR after neoadjuvant anthracycline, taxane or both[27].Â Â Â Â Â Â Â Â

Review

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ROLE OF PLATINUMS

TNBC demonstrates greater susceptibility to DNA-damaging agents like platinum than other BC subtypes. Currently pCR after neoadyuvant chemotherapy is considered a surrogate endpoint for DFS and OS in patients with TNBC. In order to improve pCR rates, various clinical trials have evaluated the role of Platinum as neoadjuvant therapy in TNBC.

A phase II (GeparSixto) trial, randomized 315 cases with stage II-III TNBC to receive weekly paclitaxel, non pegylated-liposomal A and bevacizumab (b) every 2 weeks with/without concurrent weekly carboplatin (AUC 1.5) for 18 weeks. The carboplatin group showed higher rates of pCR (53% vs. 37% P=0.005)[28]. DFS at 3 years was 85.8% in the Cb arm *vs* 76.1% in the control group (HR 0.56, P=0.0350)[29].In the CALGB)/Alliance 40603 trial, 443 cases stage II-III were treated with weekly paclitaxel for 12 weeks, followed by DD AC for four cycles, and were randomized to receive carboplatin (AUC 6) concurrently with paclitaxelÂ every 3 weeks for four cycles and/or b 10 mg/kg every 2 weeks for nine cycles. The pCR rate was significantly higher (from 41% to 54%; OR, 1.71; *P* =0.0029))[30]. DFS and OS at 39 months, did not show a statistical differenceÂ with Cb[31]. Both trials showed higher rates of hematologic toxicities and early treatment discontinuation because of toxicity. The phase 3 trial called BrighTNess, which was presented at the 2017 ASCO annual meeting, examined the impact of adding carboplatin and the poly-ADP ribose polymerase (PARP) inhibitor to the standard chemotherapy sequence of weekly paclitaxel followed by AC. The pCR rate was 31% in the control arm and 53% veliparib-Cb containing arm (*P*< .001). However, a higher pCR rate in patients who received carboplatin without veliparib was observed (58%)[32]. In this trial, patients with a BRCA mutation had a higher pCR rate than those with wild-type BRCA.

In metastatic setting, several studies further support that platinum salts may be active in advanced TNBC.Â A large phase III study compared carboplatin with T for TNBC or BRCA1/2 mutation carriers. At 11 months, there was no significant difference in PFS and OS between the two arms, although in BRCA1/2-mutated patients PFS was 6.8 months for carboplatin and 4.8 months for T[33].Â The combination of weekly paclitaxel plus carboplatin has also proved to be highly effective as first-line therapy in patients with advanced breast cancer [34]. In a phase-II study of pretreated metastatic TNBC patients, Maisano et al reported a response rate of 32%, a median PFS of 5.5 months and a median OS 11.1 months with the gemcitabine-plus-carboplatin combination[35].Â

In summary, addition of platinum to neoadjuvant

chemotherapy of TNBC seems to be a promising treatment option associated with significantly higher rates of pCR. Nevertheless, due to the increase in toxicity and the lack of clear demonstrated long-term Â survival benefit, platinum agents should not be recommended as the standard of care. Better identification of response markers to these agents is necessary. Platinum-based chemotherapy in mTNBC is associated with survival benefits and manageable toxicity.

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ANGIOGENESIS INHIBITORS

Angiogenesis is considered to be an important target for cancer therapy.Â Vascular endothelial growth factor (VEGF) is a crucial mediator in the process of angiogenesis. It is overexpressed in several neoplasias and linked to poor prognosis. Among the agents of this class, b (a humanized monoclonal antibody against all isoforms of VEGF-A) is the most widely researched; there are no prospective data that incorporation of angiogenesis inhibitors will improve OS for women with TNBC. However the use of b in this setting has been considered interesting for two reasons; one due to the lack of targeted treatments for this group. The second is due to the benefits seem in TNBC in the E2100 study [36] where 722 cases were randomized to either paclitaxel alone or with b, as initial treatment for metastasic breast cancer. The primary end point was progression-free survival (PFS) that increased significantly in the subgroup of patients with TNBC treated in the paclitaxel/BV arm (median, 10.6 Â vs. 5.9 months; HR for progression, 0.49) as well as the objective response rate (43% vs 22%). However, the OS rate was similar in the both groups.

Based on this data, the efficacy and safety of combining b with T as first-line for HER2 negative, locally advanced or metastasic disease was researched in a phase III study, AVADO[37],where 736 patients were randomized to have T 100 mg/m2 and Â placebo or b 7.5 or 15 mg/kg every 3 weeks. PFS was the primary end point and secondary end points included overall response, duration of response, time to treatment failure, OS and safety. B 15 mg/kg, (not 7.5 mg/kg) and T demonstrated higher PFS (10.1 months vs 8.2 months respectively, HR 0.77; P=.006), in the unstratified and stratified analysis, without impact on the toxicity profile of T.

The benefit of b combined with others chemotherapy treatments , includingÂ non-taxane (such a capecitabine or anthracycline-based) was evaluated in RIBBON-1 [38], a phase III, placebo-controlled study in first-line of HER2 negativeÂ metastatic breast cancer . b or placebo was infused at 15 mg/kg every 3 weeks. PFS was the primary end point and secondary ones were OS, 1-year OS, objective response rate, duration of response and safety. Median PFS was longer for each BV combination with a safety profile similar to prior phase III trials, however no statistically significant differences in OS were observed.

A meta-analysis of individual data from these phase III studies included 2447 patients[39]. This demonstrated a PFS HR of 0.63 and a OS HR of 0.96, median PFS of 8.1 months with b vs 5.4 with chemotherapy; the median OS was 18.9 vs 17.5 and OS at 1 year was 71% vs 65%.

In summary, data from the role of bevacizumab in first-line TNBC treatmentÂ indicates a PFS and response rates benefit without an OS impact. This appears to be true even when BV is administered in the adjuvant setting as we can conclude by the data of BEATRICE trial[40].However, in routine practice, the benefit must be weighed with patientsâ€™ prognosis and other therapeutic alternatives in metastatic patients, not being recommended as adjuvant treatment.

IMMUNOTHERAPY

Breast cancer has historically been considered a non-inmunogenic tumor but recent studies have demostrated that TNBC, as compared with other breast cancer subtypes, is more immunogenic. Some studies have demonstrated that the presence of tumor-infiltranting lymphocytes (TILs) were associated with better outcomes[41].

CD8+ T cells directly kill cancer cells and their presence have been associated with a better prognosis[42]. The Cancer Genome Atlas specifies that TNBC has higher PD-L1 mRNA expresion and rates of CD8+ T cell infiltration[43,44].

Pembrolizumab and nivolumab are monoclonal antibodies that target PD-1. When the antibody links to PD-1, it avoids the interaction between PD-1 on T cells and PD-L1 on tumor cells. This is how the immune response is upregulated to kill the abnormal cells[45].

PD-1 inhibitors

Pembrolizumab

Pembrolizumab given to patients with PD-L1 positive, has been evaluated in a phase I trial KEYNOTE-012 that describes evidence of clinical activity and acceptable safety profile in mTNBC[46]. The use of pembrolizumab was further evaluated in a phase II KEYNOTE-086 study that included two parts. Part one, include cohort A which had pretreated mTNBC patients, and cohort B those with PD-L1 positive and

treatment-naive. Part two is an expansion of cohort A with strongly positive neoplasias for PD-L1. The overall response rate (ORR) was 5% and 21% stable disease. The median PFS and OS were 2 and 8.9 months[47].

The ongoing phase III KEYNOTE-119 study is comparing pembrolizumab alone with physicianâ€™s choice chemotherapy (capecitabine, gemcitabine, eribuline or vinorelbine). KEYNOTE-355 is another ongoing fase III trial that evaluating pembrolizumab combination with either nab-paclitaxel, paclitaxel or carboplatin/gemcitabine compared to chemotherapy and placebo as first-line treatment in mTNBC[48].

SWOG-S1418/BR006 is a phase III study researching the safety and efficacy of adjuvant pembrolizumab for patients who had neoadyuvant chemotherapy and did not achieve pCR. Pembrolizumab combined with chemotherapy vs placebo in the neoadjuvant setting was assessed in the KEYNOTE-522 study[49].

Nivolumab

The TONIC study is an ongoing phase II for metastatic TNBC. It has got five arms. All patients had nivolumab after the induction therapy (radiotherapy, A, C, cisplatin or no induction therapy). The ORR was 22% and median duration of response was 10.9 months[50].

PD-L1 inhibitors

Atezolizumab, Avelumab and Durvalumab are monoclonal antibodies that target PD-L1. These three drugs are being investigated in the setting of metastatic and also neoadjuvant TNBC.

Atezolizumab

The initial phase I trial, which was implemented with an expansion cohort of 115 heavily preteated mTNBC, showed higher responses in PD-L1 positive (+) vs negative (-) patients (13 vs 5%). Most of the observed responses were durable, with 1-year overall survival of 100%, which is rare with standard chemotherapy[51].

In combination with chemotherapy, results of a phase I trial with weekly nab-paclitaxel were reported. The ORR was 38%, with 3% of complete responses in mTNBC patients who have received[52] 3 prior lines of chemotherapy. Responses were demonstrated in PD-L1 + and PD-L1 - cancers, but superior in PD-L1 + patients[52]. A phase III trial in first line mTNBC with this combination is currently ongoing[53].

Avelumab

The JAVELIN is a phase Ib study of Avelumab which had a cohort of 168 metastatic breast cancer, without requirement of PD-L1 expression. The ORR was 8.6% in mTNBC (N=58 patients) [54].

Durvalumab

Various trials are evaluating Durvalumab in neoadjuvant and metastatic settings, and the efficacy results are pending.

Side effects associated with the use of immunotherapy agents in BC have been consisted with those expected for this drug class. None of monotherapy trials with immunotherapy in mTNBC had improved median PFS more than historical chemotherapy regimens. A small group of patients benefits from immune-checkpoint inhibitor therapy, so predictive biomarkers are needed. Current efforts focus on developing immunotherapy combinations that can transform non-responder tumors to responders.

PARP INHIBITORS

There are two groups of DNA repair pathways depending on the existence of single-strand (SSB) or double-strand breaks (DSB). The first ones are repaired by nucleotide excision repair, base excision repair (BER) or mismatch repair, whereas DSB are repaired by nonhomologous end-joining and homologous recombination (HR) mechanisms[55].Â BRCA 1/2Â are tumor-supressor genes that encode proteins with multiple functions in cells, including a key role in the homologous recombination pathway. BRCA1 and BRCA 2 mutations were identified as causative of hereditary breast and ovarian cancers more than 20 years ago[56,57].

Prevalence of BRCA 1/2 mutations is below 5% in unselected breast cancer populations. Whereas breast carcinomas in BRCA2 mutation carriers frequently show expression of hormone receptors, most of tumors associated to a BRCA1 mutation display a triple negative breast cancer (TNBC) profile[58]. Identification of BRCA1 mutations in the TNBC population reaches percentages higher than 10-15% in several case-series[59-61]. Furthermore, a small proportion ofÂ BRCA1/2-negative TNBCs show a deficiency in DNA repair via homologous recombination, a phenotype known as BRCAness. Different mechanisms for BRCAness have been described, as defects in other genes that modulate HR, epigenetic BRCA1 promoter hypermethylation or somatic mutations in BRCA1/2[62,63].Â

Members of PARP family are crucial to repair DNA SSBs through the BER mechanism. PARP inhibitors were originally developed with the objective of sensitizing tumor cells to conventional treatments that disrupt the DNA[64].Presence of deleterious BRCA mutations confers sensitivity to DNA cross-linking agents and PARP inhibitors by different mechanisms, such as lethality resulting from permanent DNA

damage and the replication stop due to physical block of replication forks by PARP trapping. Olaparib, one of the most widely investigated PARP inhibitors, offered clinical benefit in phase 1 and 2 trials involving patients with gBRCAm breast, ovarian, pancreatic, or prostate cancers[65-68].

Treatment with PARP inhibitors has been specially succesful in high grade-serous ovarian carcinomas. Analysis of 489 of these tumours by the Cancer Genome Atlas Research Network has revealed that homologous recombination is defective in about half of them[69].So that, activity of these drugs is not limited to ovarian cancer patients with a mutation in BRCA1/2 genes[70].

Several PARP inhibitors have been developed, including Olaparib (AZD2811), Niraparib (MK-4827), Rucaparib (AG-014699), Veliparib (ABT-888), Talazoparib (BMN673) and E7449/2X-121. Olaparib is the only one with published results of a phase 3 trial in breast cancer patients. The OlympiAD trial randomised 302 patients in a 2:1 ratio to olaparib (300 mg twice daily) or standard treatment with chemotherapy (capecitabine, eribuline or vinorelbine at the discretion of the investigator)[71].Patients included had HER2 negative metastatic breast cancer with two or less previous chemotherapy regimens for advanced disease. They should have received antracyclines and taxanesÂ (unless it was contraindicated) and at least one endocrine regimen in case of hormone-receptor positive breast cancer. If platinum was previously administered in the (neo)adjuvant or metastatic setting, a DFS of 12 or more months or no evidence of progression during treatment, respectively, were required. The primary objective of the trial was PFS, that was significantly improved in the olaparib arm (7.0 vs. 4.2 months; HR for disease progression or death, 0.58; 95% confidence interval [CI], 0.43 to 0.80; P< 0.001).The response rate was also higher with olaparib (59.9% vs. 28.8%), although no difference in OS was detected. There were less grade >/= 3 adverse events in the olaparib group, the most common of them was anemia.

Currently there are several ongoing trials with olaparib and other PARP inhibitors in breast cancer and other solid neoplasms. Research should focus not only on the efficacy of these drugs, but also on the recognition of biomarkers of response, mechanisms of resistance and the role of combining with other therapies[72].

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Androgen receptor blockade

Androgen receptors (AR) are expressed in most breast cancers but despite this fact, AR antagonists are not standard practice as therapy[73].

In TNBC, the level of AR expression is varied depending on the assay methodology, cutoff for positivity and patient population.

Some studies have suggested that higher level of AR expression is linked to improved outcomes, with earlier clinical stage, lower histologic grade and lower mitotic score[74,75].Â Â Â

However, controversy is served as other studies show just the opposite.

Hu *et al* have showed that AR expression was associated with higher mortality among women with TNBC[76].Â

Similar results were shown by Park *et al*. These authors reported that AR was significantly linked to favourable characteristics in breast tumours and to improved results in ER-positive but not in ER-negative tumours. They concluded that AR is probably another marker for endocrine responsiveness in ER-positive tumours and a target for treatment of ER-negative tumours[77].

Other authors have found that AR is a negative prognostic factor for OS especially in lymph node-negative subgroup. However, its prognostic value was not observed in TNBC with lymph node involved or tumours larger than 2cm[78].

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These differences among studies could be due to variations in sample sizes, sensitivity of the primary or an overlap between AR and molecular apocrine signatures in TNBC.

Molecular apocrine tumours are a poorer prognostic subgroup of TNBC with AR expression and AR pathway activation. Studies of gene expression have shown that these tumours have a paradoxical expression of genes typically expressed in ER-positive as a consequence of AR-driven transcription of the ER pathway[79,80].Â

The first clinical studies to investigate targeting AR as therapy in advanced breast cancers were carried out in the 80s.

Flutamide, an oral antiandrogen, was evaluated in advanced breast cancer but did not show any meaningful benefit[81,82].

More recently, a phase II study has explored bicalutamide (an AR antagonist) in AR-positive, ER/PR negative metastatic breast cancer. AR IHC > 10% nuclear staining is positive and if the primary or a metastatic area are positive, patients could receive

bicalutamide at a dose of 150 mg daily.

424 patients with ER/PR negative breast cancers were screened for AR and 12% tested AR-positive. The authors reported a 19% of clinical benefit ratio with bicalutamide although there were no objective responses[83].

Enzalutamide is a novel potent and competitive targeted AR inhibitor. It avoids the translocation of AR from the cytoplasm to the nucleus and blocks the binding of AR to chromosomal DNA and results in stopping the transcription of tumour genes[84].

Traina *et al* published a phase II trial with enzalutamide in advanced TNBC AR positive. IHC results suggest that AR prevalence is higher than previously reported.

47% of patients had an androgen-related gene signature and clinical outcomes were superior in this group. 118 cases with metastatic TNBC AR positive had a clinical benefit rate of 35%. Authors concluded that enzalutamide may represent a novel therapeutic option in these patients[85].Â

Tumours from responders to enzalutamide had a distinct genomic signature associated to androgen biology. This led to the development of a predictive assay named Predict-AR. This demonstrates the potential to predict clinical response to enzalutamide in TNBC and may be helpful to select TNBC patients for future studies with enzalutamide[86].

Patients with tumours Predict-ARâ€“positive had a clinical benefit ratio of 36% at 6 months compared to only 6% in Predict-ARâ€“negative[85].

All these results encourage the identification of patients with AR positive so further trials could be carried out to get definitive conclusions.

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Anti-EGFR therapies

EGFR is overexpressed in many TNBC and it could be a therapeutic target. EGFR inhibitors are small molecular tyrosine kinase inhibitors (TKI) and monoclonal antibodies (mAb). Although available for other cancers (non-small cell lung cancer and colorectal cancer), in breast neoplasias, the results have not been encouraging.

However, a small group of patients have shown benefits with these and this is the reason to suggest a better stratification of patients with TNBC to identify the best candidates for these and to design a better combination for this group[86,87].

MET and EGFR receptors are highly expressed in TNBC and as such those are actionable targets. Crosstalk between MET and EGFR is involved in resistance to single agent (MET or EGFR inhibitors) in various cancers. Â

Therefore dual inhibition of MET and EGFR is probably needed.

It has been reported that a MET and EGFR inhibitors combination with MGCD265/erlotinib or crizotinib/erlotinib is very effective in stopping tumour growth and reduces the variability in therapeutic response compared to monotherapy[87].

Authors concluded that a combination of MET and EGFR inhibition could be a promising future treatment for TNBC[87].

Conclusion

There is a clear need for improvement in treatment alternatives that could be useful in primary and metastatic TNBC.

Current therapeutic options are restricted to chemotherapy, so this is not the time to leave it behind; however, other agents are promising such as PARP inhibitors and tyrosine kinases. More research is ongoing and hopefully soon chemotherapy could be part of the past.