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SHORT COMMUNICATION

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Immunotherapy: The end of the "dark age" for metastatic triple-negative breast cancer?

Michela Palleschi MD | Roberta Maltoni MD | Samanta Sarti MD | Elisabetta Melegari MD | Sara Bravaccini PhD | Andrea Rocca MD

Istituto Scientifico Romagnolo per lo Studio e la Cura dei Tumori (IRST) IRCCS, Meldola, Italy

Correspondence
Michela Palleschi, Istituto Scientifico Romagnolo per lo Studio e la Cura dei Tumori (IRST) IRCCS, Via Maroncelli 40, 47014 Meldola, Italy.
Email: michela.palleschi@irst.emr.it

Abstract

The lack of effective therapies for metastatic triple-negative breast cancer (mTNBC) highlights the need for the development of novel treatment strategies. The cornerstone of treatment has long been represented by chemotherapy. Relevant evidence has recently emerged regarding the efficacy of immune checkpoint inhibitors, with the demonstration of a statistically significant improvement of progression-free survival with the addition of atezolizumab to nab-paclitaxel in the first-line treatment of mTNBC, accompanied by a substantial overall survival benefit in the PD-L1-positive subgroup. Despite this, it is necessary to identify the biomarkers that could allow a better selection of patients and combination regimens.

KEYWORDS

biomarkers, immune checkpoint inhibitors, metastatic triple negative breast cancer

Triple-negative breast cancer (TNBC) accounts for about 15% of newly diagnosed breast cancer (BC) cases.[1] TNBC is a heterogeneous disease with distinct molecular subtypes, showing different prognoses and different responsiveness to chemotherapy and target agents. Some rare histopathological subtypes, such as medullary, metaplastic, apocrine, and adenocystic, are typically triple negative. In the last decade, genomic analyses have demonstrated the inter and intratumoral heterogeneity of TNBC and identified "molecular subtypes" including basal-like 1 and 2, mesenchymal, and luminal androgen receptor.[2]

TNBC recurrences, mainly visceral, are relatively common within 2-3 years, and the absence of recurrence up to 5 years suggests a low risk of subsequent distant metastases.[3] The median OS for metastatic patients with TNBC is about 12 months with conventional cytotoxic agents, accompanied by considerable toxicity.

The poor prognosis and the lack of targeted therapies for patients with TNBC have fostered a considerable effort to discover viable molecular targets to treat them.

The immune tumor microenvironment has been shown to play a crucial role in the development and progression of cancer. Evading anti-tumor immunity is a hallmark for the development and progression of cancer.[4] This is commonly due to the activation of checkpoints that dampen the immune response, among which programmed death 1 (PD-1) and cytotoxic T-lymphocyte antigen 4 (CTLA4) have emerged as the most important.

The tumors can create an immunosuppressive microenvironment also by recruiting specific immune cells that promote tumor growth and progression. Elevated levels of CD4 + regulatory T cells (Treg) are associated with poor prognosis. For instance, Forkhead box P3-positive (FOXP3+) Treg cells are crucial for inducing and maintaining tolerance to autoantigens. The expression of FOXP3 in BC was associated with a worse metastasis-free survival, with increased risk with the growing intensity of FOXP3 immunostaining.[5]

Immunotherapy yields the best responses in tumors defined as "inflamed," where dendritic cells are abundant and T-lymphocytes are predominantly CD8 + cytotoxic effectors. The percentage of BCs that could be considered "inflamed" is relatively small compared with other cancers and varies substantially between subtypes.[6] Nevertheless, targeting the immune system in BC is supported for example by the improvements in overall survival in HER2-positive BC with the use of monoclonal antibodies directed against HER2, which act at least partially inducing an immune response. There are strong pieces of evidence in early BC that higher pathologic response rate after neo-adjuvant chemotherapy and a good survival outcome

were associated with higher tumor-infiltrating lymphocytes (TIL) levels, indicating a likely robust and effective immune response in the tumor microenvironment. [7]

PD-1 is an immune checkpoint receptor, inhibiting immune response. Its ligand, programmed death-ligand 1 (PD-L1), is expressed both in BC cells and in TILs, with higher levels associated with younger age, high grade, lack of ER expression, and triple-negative phenotype, particularly the basal subtype.

Immune checkpoint inhibitors (ICI) represent a recent critical discovery in the malignant diseases treatment, including BC, with a new approach for the treatment of TNBC. Food and Drug Administration (FDA) approved several agents, which include blocking antibodies for CTLA4 (ipilimumab and tremelimumab), PD-1 (nivolumab, pembrolizumab, and cemiplimab), and PD-L1 (durvalumab, avelumab, and atezolizumab) thanks to promising results in the therapy of melanoma and of lung, kidney, colorectal, head and neck, and bladder cancers. Durable responses and long-term survival benefit have been experienced by many cancer patients with favorable toxicity profiles of immunotherapeutic agents relative to chemotherapy.[8]

In studies of single-agent anti-PD-1/ PD-L1 immunotherapy in BC, the highest responses were observed in patients with untreated metastatic TNBC. These results suggest that ICI should be more active in untreated patients, suggesting testing at an early stage of TNBC.

Currently, several clinical trials are evaluating combinations of chemotherapy plus immunotherapy in patients with TNBC. The IMpassion-130 compared nab-paclitaxel plus atezolizumab to nab-paclitaxel plus placebo in patients with untreated advanced TNBC, reporting a statistically significant progression-free survival benefit in the intent-to-treat (ITT) population (hazard ratio [HR] for progression or death 0.80, 95% confidence interval [CI] 0.69-0.92, $P = .002$), as well as in the PD-L1-positive subgroup (HR 0.62, 95% CI 0.49-0.78, $P < .001$).[9] At ASCO 2019, Schmid and colleagues updated the overall survival (OS) results, reporting a 7-month improvement in median OS in the PD-L1-positive subgroup (25.0 vs 18.0 months, HR 0.71, 95% CI: 0.54-0.93).[10] As OS was not significantly improved in the ITT population, and because of the planned hierarchical OS testing, first in the ITT population and then in the PD-L1-positive subgroup, the trial cannot formally claim an OS gain. Nonetheless, the study underscores the importance of adding a checkpoint inhibitor to standard chemotherapy for first-line treatment for metastatic TNBC in the PDL-1 positive subgroup. Moreover, the objective response rate (ORR) was numerically higher following the addition of atezolizumab in both the ITT population (56% vs 46%) and the PD-L1 + population (59% vs 43%), and more complete responses have been observed with atezolizumab than without (ITT, 7% vs 2%; PD-L1 + population, 10% vs 1%).

In light of these encouraging data, on March 18, 2019, the FDA granted accelerated approval to atezolizumab plus nab-paclitaxel for the treatment of adults with unresectable, locally advanced, or metastatic, PD-L1–positive, TNBC.

With the limits of cross-trial comparisons, benefit from atezolizumab + nab-paclitaxel in the PD-L1-positive subgroup compares well with that from other regimens as first-line therapy for metastatic TNBC[11] (Table 1).

The choice of the accompanying drug in combination regimens should preferably be based on tumor biomarkers and molecular subgroups, to identify the patient populations most likely to benefit.[12] Chemotherapy can have an immunomodulatory effect and induce many changes in the tumor microenvironment; these changes could positively influence the efficacy of immunotherapy. In particular, several chemotherapy drugs, usually used in the TNBC treatment, can induce distinct effects on the immune system.[13]

The ICI approach is fascinating, given the encouraging results of long-term survival potential, but it is essential to readily recognize immune-related adverse events (irAE) for its safe use. The most frequent irAEs, reported in published BC-ICI trials, are rash and pruritus (up to 18%), thyroid disorders (up to 12%) and liver function abnormalities (up to 10%). To prevent severe and potential permanent sequelae or therapy interruption, early recognition and timely treatment of these specific adverse events are essential. The consensus guidelines are a useful resource for the management of these adverse events.[14]

The identification of surrogate markers of ICI's efficacy is clinically meaningful and highly required, due to the treatment's costs and the potential incidence of irAEs.

TABLE 1 Different chemotherapy regimens as first-line therapy for mTNBC

Chemotherapy regimen	ORR	PFS (median)	OS (median)
Taxane monotherapy	23%-36%	4.5-5.4 mo	12.3 mo
Platinum salt monotherapy	23%-35%	2.9-3.1 mo	11.0-12.4 mo
Capecitabine monotherapy	NR	4.2 mo	NR
Paclitaxel plus gemcitabine	49%	6.5 mo	NR
Platinum plus gemcitabine	30%-64%	4.6-7.7 mo	12.6 mo
Taxane plus bevacizumab	49%	7.2 mo	18.3 mo
Chemotherapy plus bevacizumab (meta-analysis)	42%	8.1 mo	18.9 mo
Maintenance capecitabine plus bevacizumab (Imelda)	NR	7.6 mo	NR
Nab-paclitaxel + atezolizumab (IMpassion 130)	56%	7.2 mo	21.3 mo
Nab-paclitaxel + atezolizumab (IMpassion 130) in PDL1 + subgroup	58.9%	7.5 mo	25.0 mo

Only about 10% of BC show expression of PD-L1, either measured on tumor cells or on TILs, with higher rates in TNBC. Contrary to other tumor types, PD-L1 expression on tumor cells is not a valid predictive biomarker of ICI efficacy in BC. Actually, PD-L1 in IMpassion trials is assessed on infiltrating immune cells and measured as the fraction of positive immune area in relation to the whole tumor area, considering as positive tumors with expression on ≥1%.[9,15]

Tumor mutational burden (TMB) is associated with clinical benefit to immune checkpoint blockade in patients with melanoma, lung, and colon cancer.[16] A higher TMB is more frequent in TNBC as compared to hormone receptor-positive subtypes; despite this, in BC, TMB was not demonstrated as a predictor of ICI efficacy.[17]

Microsatellites (MS) are tandem repeats of short DNA sequences, abundant throughout the human genome. Microsatellite instability (MSI) is a hypermutator phenotype that occurs in tumors with impaired DNA mismatch repair (MMR). Recently, pembrolizumab has been shown to be active in tumors harboring a high MSI, leading to its approval for MMR-deficient unresectable or metastatic solid tumors. MSI incidence in BC has not yet been fully elucidated, but seems to be less frequent than 2%.[18]

BRCA mutations predispose to TNBC, being discovered in 40%-50% of cases. The FDA approved poly(ADP-ribose) polymerase (PARP) inhibitor agents for the treatment of advanced BRCA-mutant BCs. BRCA mutations cause impairment of homologous recombination, the high fidelity DNA repair mechanism; impairing a second DNA repair mechanism, such as the base excision repair through PARP inhibition, leads to accumulation of DNA damage and mutations, yielding "synthetic lethality" of tumor cells but also possible induction of neoantigens. Therefore, PARP inhibitors are interesting as combination partners for ICI. In vivo, combining PARP inhibitors with ICI has shown augmented effector T cell function. Newly, the combination of olaparib with durvalumab and the combination of niraparib with pembrolizumab, in germline BRCA-mutated metastatic TNBC, showed a clinical activity.[19]

As already underlined, TNBC is thought to be more immunogenic than other BC, and AR + TNBC shows a higher frequency of PD-L1 expression. Guiu et al suggest a negative prognostic impact of AR+/FOXA1 + phenotype in nonmetastatic TNBC, discovering a higher rate of PD-L1 expression in the AR+/FOXA1- subgroup. Among patients with PD-L1 + tumor, they found significantly poorer RFS and OS in case of AR/FOXA1 co-expression.[20] It could be interesting to evaluate the benefit from the association of anti-PD1 or PD-L1 therapies with an antiandrogen in this particular subgroup of patients.

Given the encouraging results in first-line treatment of metastatic TNBC, ICIs are being tested also in the neo-adjuvant and adjuvant settings.

The approval of the first combination of chemo-immunotherapy for metastatic TNBC is a decisive step forward in the treatment of this disease. Toxicities must be balanced with benefits, especially given the promise of lasting response and better survival. The identification and use of predictive biomarkers could allow a better selection of patients and combination regimens to further improve results and cost-effectiveness of immune checkpoint inhibitors in metastatic TNBC.

CONFLICT OF INTEREST

Michela Palleschi, Roberta Maltoni, Samanta Sarti, Elisabetta Melegari, Sara Bravaccini have no conflicts of interest to declare. Andrea Rocca received travel grant and invitation for advisory from Novartis, Roche, and Lilly.

ORCID

Michela Palleschi https://orcid.org/0000-0003-2623-4705

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