



Triple negative breast cancer: emerging light on the horizon—a narrative review

Umangjot K. Bharaj¹, Ana E. Lohmann², Phillip S. Blanchette²

¹Schulich School of Medicine, University of Western Ontario, London, ON, Canada; ²Department of Oncology, London Regional Cancer Program, London Health Sciences Centre, University of Western Ontario, London, ON, Canada

Contributions: (I) Conception and design: All authors; (II) Administrative support: None; (III) Provision of study materials or patients: None; (IV) Collection and assembly of data: UK Bharaj, PS Blanchette; (V) Data analysis and interpretation: UK Bharaj, PS Blanchette; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

Correspondence to: Dr. Phillip S. Blanchette. 800 Commissioners Road East, London, ON N6A 5W9, Canada. Email: phillip.blanchette@lhsc.on.ca.

Abstract: Triple negative breast cancer (TNBC) continues to be an aggressive disease entity associated with poor survival outcomes. The mainstay of treatment has historically been cytotoxic chemotherapy treatment. However, promising novel therapies including immunotherapy agents, antibody-drug conjugates, poly (ADP-ribose) polymerase (PARP) inhibitors and targeted therapies are emerging. In recent clinical trials, these various treatment modalities have demonstrated improvements in progression-free and overall survival in select patient populations. Specifically, the IMpassion130 and KEYNOTE-355 clinical trials observed a significant survival advantage among TNBC patients treated with immune checkpoint inhibitors and chemotherapy who were program death receptor ligand-1 (PD-L1) positive. Sacituzumab govitecan, a novel antibody drug conjugate, also has demonstrated an impressive overall survival result in previously heavily pre-treated TNBC patients. Targeted therapies such as PARP inhibitors, AKT inhibitors and androgen receptor antagonists may also have modest clinical activity and benefit for select patients. Future studies combining promising targeted therapies, cytotoxic agents and immunotherapy drugs are currently underway. Despite recent clinical trial successes, disease heterogeneity and limited access to molecular testing and novel therapies continue to be barriers in routine clinical practice. Nonetheless, we are optimistic that recent advances in clinical trial research will soon lead to significant improvement in the quality of care and survival for patients diagnosed with TNBC.

Keywords: Triple negative; breast cancer; metastatic; novel therapies

Received: 16 December 2020; Accepted: 26 February 2021; Published: 30 June 2021.

doi: 10.21037/pcm-20-75

View this article at: <http://dx.doi.org/10.21037/pcm-20-75>

Introduction

Triple negative breast cancer (TNBC) is a particularly aggressive type of breast cancer defined by negative immunohistochemistry staining for the estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth receptor 2 (HER2). TNBC accounts for approximately 20% of breast cancer diagnoses and is associated with early age of onset, aggressive disease biology and poor survival (1). Advanced TNBC has been historically managed with various cytotoxic chemotherapy agents.

TNBC is not a singular type of breast cancer, but rather a heterogeneous mix of various cancer subtypes (2,3). An updated categorization of TNBC separates the disease into four subtypes: (I) luminal androgen receptor (LAR), (II) basal-like, (III) immune-enriched, and (IV) mesenchymal based on genomic profiling (4). There are a number of new promising new therapies in TNBC that are currently being researched with varying degrees of success, including: (I) immune-directed therapy with checkpoint inhibitors, (II) antibody-drug conjugates, (III) PARP inhibitors, and (IV) targeted therapies including agents inhibiting cell signaling

Table 1 Immune checkpoint inhibitor therapy in combination with chemotherapy for metastatic triple negative breast cancer among patients defined as PD-L1 positive—summary of updated results

Trial Name	Intervention	N	PD-L1	PFS	OS
IMpassion130 (Emens <i>et al.</i>) (5)	Nab-paclitaxel and atezolizumab	369	PD-L1 (IC $\geq 1\%$)	7.5 (experimental arm) vs. 5.0 months (control arm); HR =0.62 (95% CI: 0.49–0.78)	25.4 (experimental arm) vs. 17.9 months (control arm); HR=0.67 (95% CI: 0.53–0.86)
IMpassion131 (Miles <i>et al.</i>) (6)	Paclitaxel and atezolizumab	292	PD-L1 (IC $\geq 1\%$)	6.0 (experimental arm) vs. 5.7 months (control arm); HR =0.82 (95% CI: 0.60–1.12)	22.1 (experimental arm) vs. 28.3 months (control arm); HR=1.12 (95% CI: 0.76–1.65)
KEYNOTE-355 (Cortes <i>et al.</i>) (7)	Chemotherapy and pembrolizumab	323	PD-L1 (CPS $\geq 10\%$)	9.7 (experimental arm) vs. 5.6 months (control arm); HR =0.65 (95% CI: 0.49–0.86)	NA

CI, confidence interval; CPS, combined positive score; HR, hazard ratio; IC, tumor infiltrating immune cells; N, number; NA, not available; OS, overall survival; PD-L1, program death receptor ligand-1; PFS, progression-free survival.

through the androgen receptor (AR) or PIK3/AKT/mTOR pathway. Combination therapies among these classes of agents are also under investigation.

Novel therapies for TNBC are now demonstrating progression-free and modest overall survival (OS) benefits in some cases indicating a possible “light on the horizon”. Despite the emerging therapies, significant work to develop safer and more effective treatments for this aggressive form of breast cancer is warranted. We present the following article in accordance with the narrative review checklist (available at: <http://dx.doi.org/10.21037/pcm-20-75>).

Immunotherapy

There appears to be a net clinical benefit in combining immune checkpoint inhibitors and traditional cytotoxic chemotherapy for TNBC patients whose cancers are positive for program death receptor ligand-1 (PD-L1) expression. This is based on the cumulative data from the IMpassion130 and KEYNOTE-355 clinical trials outlined in *Table 1* (5-8). The IMpassion130 clinical trial randomized patients to receive nab-paclitaxel plus or minus atezolizumab, a fully humanized monoclonal antibody targeted against PD-L1 (5,8). The recently updated results show significant increase in progression-free survival (PFS) [7.5 *vs.* 5.0 months, hazard ratio (HR) =0.62, 95% confidence interval (CI): 0.49–0.78] and OS (25.4 *vs.* 17.9 months, HR =0.67, 95% CI: 0.53–0.86) among patients whom are PD-L1 positive (5). This is in contrast to a negative study IMpassion131 investigating paclitaxel and atezolizumab (6). These diverging results remain an area of controversy but could reflect differences in the chemotherapy backbone, steroid

pre-medication requirements, baseline patient characteristics or statistical chance. Nonetheless, the KEYNOTE-355 clinical trial which randomized advanced TNBC patients to receive either physician choice chemotherapy plus or minus pembrolizumab (a fully humanized monoclonal antibody targeted against PD-1) has also reported a significant improvement in progression-free survival among patients with PD-L1 positive expression (PFS) (9.7 *vs.* 5.6 months, HR =0.65, 95% CI: 0.49–0.86) (7). Final OS results are awaited but current results are highly suggestive this will be a positive trial.

The IMpassion130 and KEYNOTE-355 trials used different PD-L1 diagnostic assays (PD-L1 SP142 Ventana IHC assay *vs.* PD-L1 22C3 pharmDx IHC assay) with their own distinct scoring systems [(I) PD-L1 expression of tumor infiltrating immune cells (IC) as percentage of tumor area versus (II) PD-L1 expression measured by the combined positive score (CPS); defined as the ratio of PD-L1 positive tumor cells (tumor cells, lymphocytes and macrophages) divided by the total number of tumor cells multiplied by 100] (9,10). The definition of PD-L1 positivity also varies according to the diagnostic test used for either atezolizumab (PD-L1-positive: IC $\geq 1\%$) and pembrolizumab (PD-L1 positive: CPS $\geq 10\%$). Results from both the IMpassion130 and KEYNOTE-355 clinical trials did not show any significant benefit from immune checkpoint inhibitor and chemotherapy among TNBC patients whose PD-L1 testing was negative (IC $< 1\%$ or CPS $< 1\%$). The KEYNOTE-355 was the only study showing benefit in the intention to treat (ITT) population irrespective of PD-L1 testing.

Presently, we have a great deal to learn to optimize the use of immunotherapy in breast cancer. Currently, early

Table 2 PARP inhibitor therapy in metastatic breast cancer—summary of updated results

Trial name	Intervention	N	BRCA	PFS	OS
OlympiAD (Robson <i>et al.</i>) (20)	Olaparib monotherapy	302 (50% TNBC)	gBRCA	7.0 (experimental arm) vs. 4.2 months (control arm); HR =0.58 (95% CI: 0.43–0.80)	19.3 (experimental arm) vs. 17.1 months (control arm); HR =0.90 (95% CI: 0.66–1.23)
EMBRACA (Litton <i>et al.</i>) (21)	Talazoparib monotherapy	431 (44% TNBC)	gBRCA	8.6 (experimental arm) vs. 5.6 months (control arm); HR =0.54 (95% CI: 0.41–0.71)	19.3 (experimental arm) vs. 19.5 months (control arm); HR =0.85 (95% CI: 0.67–1.07)
BROCADE3 (Dieras <i>et al.</i>) (22)	Veliparib and chemotherapy	509 (48% TNBC)	gBRCA	14.5 (experimental arm) vs. 12.6 months (control arm); HR =0.71 (95% CI: 0.57–0.88)	33.5 (experimental arm) vs. 28.2 months (control arm); HR =0.95 (95% CI: 0.73–1.23)

CI, confidence interval; gBRCA, germline BRCA mutation; HR, hazard ratio; N, number; OS, overall survival; PFS, progression-free survival; TNBC, triple negative breast cancer.

introduction of an immune checkpoint inhibitor as part of 1st line systemic therapy in combination with chemotherapy appears to be a favorable strategy. Immune check-point inhibitor therapy used in subsequent later lines of treatment or as a single agent appears less effective. Further studies are needed to determine the optimal chemotherapy backbone and whether combination therapy with other antibody drug conjugates or targeted therapies may have superior effectiveness. Initial trials are showing the “tail of the curve” phenomenon whereby a small proportion of patients are experiencing significant durable clinical benefit over many months (11). PD-L1 testing harmonization and the development of improved biomarkers to predict immune response are needed. We should also investigate strategies to render tumors more immunogenic, such as immune priming with radiation therapy (12). Studies combining immunotherapy agents are warranted and the development of adoptive immunotherapy strategies including chimeric antigen receptor (CAR) T-cell therapy are under early development (13–15). Overall, the results from immune checkpoint inhibitor therapies are promising and likely will represent a new standard of care treatment for selected immune responsive patients with advanced TNBC.

Antibody-drug conjugates

The most impressive advancement to date in triple negative breast cancer appears to be related to sacituzumab govitecan, an antibody drug conjugate consisting of a monoclonal antibody directed at trophoblast cell-surface antigen-2 (TROP-2) conjugated to SN-38, a topoisomerase I inhibitor and active metabolite of irinotecan. In the ASCENT trial, sacituzumab govitecan was evaluated among heavily pre-

treated advanced triple negative breast cancer patients compared against physician choice chemotherapy (eribulin, vinorelbine, gemcitabine or capecitabine) (16). Updated results were recently reported at the European Society of Medical Oncology (ESMO) 2020 virtual meeting showing both significantly improved PFS (5.6 *vs.* 1.7 months, HR =0.41, 95% CI: 0.32–0.52, $P<0.0001$) and OS (12.1 *vs.* 6.7 months, HR =0.48, 95% CI: 0.38–0.59, $P<0.001$) (17). In a heavily pre-treated population, the overall response rate was 35% and clinical benefit rate (CBR) was 45%. Toxicity was manageable with the most common side effects being fatigue, myelosuppression, nausea and vomiting, diarrhea and alopecia. Further quality of life data and the final study publication are eagerly awaited. Exploratory Phase II studies of sacituzumab govitecan in combination with immunotherapy (Pembrolizumab: NCT04468061) and PARP inhibition (Talazoparib: NCT04039230) are currently underway investigating potential safety and synergy of combining these various agents. Studies in newly diagnosed and adjuvant triple negative breast are also likely warranted given the promising activity of this compound. Another antibody drug conjugate, Ladirtuzumab vedotin, is also showing promise in earlier phase clinical trials (18).

PARP inhibitors

BRCA1 or *BRCA2* mutated TNBCs are sensitive to poly(ADP-ribose) polymerase (PARP) inhibitors and platinum chemotherapy due to a deficiency in homologous recombination repair of DNA damage (19). Clinical trials among patients positive for germline BRCA mutations investigating various PARP inhibitors (olaparib, talazoparib and veliparib) are outlined in *Table 2* (20–24). These

clinical trials investigated various PARP inhibitors either as monotherapy or combined with chemotherapy. The results have demonstrated clinically significant improvements in progression-free survival, especially in subgroup analysis targeting TNBC. Quality of life benefits have also been reported, however, no significant improvements in OS have been observed to date (25,26). A recent presentation at the virtual ASCO 2020 annual meeting indicates a trend towards improved OS among patients with germline BRCA mutation carriers treated with cisplatin and veliparib versus chemotherapy alone (OS: 13.7 *vs.* 12.1 months; HR =0.66, P=0.14) (27). Recent studies have also indicated that PARP inhibitors may also benefit patients with somatic BRCA mutations and other homologous recombination defects or BRCA-like mutations (28). PARP inhibitors are also being tested in combination with immune check-point inhibitors and the results from these studies are eagerly awaited. PARP inhibitors may modulate the immune tumor microenvironment and increase genomic instability which may potentially increase responsiveness to immune checkpoint inhibitor therapy (29). Overall, timely access to BRCA testing in advanced TNBC patients has limited more widespread use of PARP inhibitor therapy.

Targeted therapy

Targeted therapy to date has only shown very modest success in the management of TNBC. One of the most investigated strategies has been targeting blockage of the AR. Phase II clinical trials have been conducted using bicalutamide, abiraterone acetate and enzalutamide. The AR is positive positivity in approximately 20% of triple negative breast cancer cases and current phase II studies have demonstrated CBR ranging from 19–25% and median PFS of 3 months (30–32). To date, strategies targeting the AR have not made any large-scale impact in the treatment of triple negative breast cancer, although studies combining androgen blockade with other novel agents are underway.

Several recent studies have also reported on the utility of AKT inhibitors in advanced TNBC. The results of the LOTUS study investigating ipatasertib (an oral AKT inhibitor) to paclitaxel for the first line treatment in inoperable locally advanced or metastatic TNBC showed a significant PFS advantage (6.2 *vs.* 4.9 months; HR =0.60, 95% CI: 0.37–0.98; P=0.037) and a trend towards improved OS (25.8 *vs.* 16.9 months, HR =0.80, 95% CI: 0.50–1.28) (33,34). Another AKT inhibitor Capivasertib in combination with paclitaxel also has showed similar results

in the PAKT study (PFS: 5.9 *vs.* 4.2 months, HR =0.74, 95% CI: 0.50–1.08, P=0.06; OS: 19.1 *vs.* 12.6 months, HR =0.61, 95% CI: 0.37–0.99, P=0.04) (35). The PAKT trial suggests that the benefits of AKT inhibition might be largely limited to the subgroup of patients with PIK3CA/AKT1/PTEN alterations, although an OS benefit cannot be excluded in patients with non-mutated tumors. We await the confirmatory Phase III IPATunity130 (NCT03337724) and CAPItello-290 (NCT03997123) which are ongoing. Other novel agents targeting a variety of cell signaling pathways are also being explored to determine their activity in TNBC.

Conclusions

Overall, recent clinical trials have indicated a number of promising therapies for selected patients with metastatic TNBC or locally advanced TNBC. The heterogeneity of the disease remains a significant barrier and improved molecular testing and biomarkers to predict response to immunotherapy are needed.

PD-L1 positive patients should be considered for 1st line therapy with nab-paclitaxel and atezolizumab while patients carrying germline BRCA1/2 mutations may derive benefit from PARP inhibition. For the remaining patients, standard chemotherapy such as taxanes, anthracyclines, capecitabine, eribulin and platinum agents should be considered. In later line therapy, sacituzumab govitecan presents a very promising novel treatment option with a significant survival advantage.

As we move ahead, a number of studies combining novel targeted agents, antibody drug conjugates and immunotherapy are underway. Additionally, combination immunotherapy trials and adoptive immunotherapy strategies will also hopefully add further benefit in the years ahead. Improving feasibility and access to genomic and additional biomarker testing is critical to identify patients who may significantly benefit from either targeted and immunotherapy treatment strategies as opposed to traditional chemotherapy. While progress in the advancement of treatment for TNBC has been very slow, there is new hope on the horizon, and we look forward to further scientific, research and clinical advances which hold the potential to meaningfully improve the quality of care and survival for TNBC patients and their families.

Acknowledgments

Funding: None.

Footnote

Provenance and Peer Review: This article was commissioned by the Guest Editor Jacques Raphael for the series “Management of Triple Negative Breast Cancer” published in *Precision Cancer Medicine*. The article has undergone external peer review.

Reporting Checklist: The authors have completed the Narrative Review Checklist. Available at <http://dx.doi.org/10.21037/pcm-20-75>

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at <http://dx.doi.org/10.21037/pcm-20-75>). The series “Management of Triple Negative Breast Cancer” was commissioned by the editorial office without any funding or sponsorship. AL received research funding (in kind) from Epic Sciences, outside the submitted work. The authors have no other conflicts of interest to declare.

Ethical Statement: The author is accountable for all aspects for the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved

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doi: 10.21037/pcm-20-75

Cite this article as: Bharaj UK, Lohmann AE, Blanchette PS. Triple negative breast cancer: emerging light on the horizon—a narrative review. *Precis Cancer Med* 2021;4:12.