A Structured Review of Novel Therapies in the Treatment of Triple Negative Breast Cancer

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Abstract

Triple negative breast cancer (TNBC) is a heterogenous disease, that tends to occur in younger women and carries a poor prognosis, with early relapse rates and metastasis is common. For a long time, there has been limited treatment options with systemic chemotherapy being the therapeutic mainstay. TNBC has been classified into different molecular subtypes.

This review focuses on advances in the treatment of TNBC and the potential therapies with promising future in both the early and advanced stages. Recent studies have shown the efficacy of immunotherapy agents and poly (ADP-ribose) polymerase inhibitors in the treatment of metastatic TNBC. Immune checkpoint inhibition by programmed cell death ligand 1 (PD-L1) inhibitors in combination with systemic chemotherapy, have been of particular benefit in subpopulations whose tumours express PD-L1, altering the course of the disease significantly. There are multiple other new agents currently in development for the treatment of TNBC, with the most promising being: AKT inhibitors, Sacituzumab Govitecan and androgen receptor inhibitors.

Keywords: Triple-negative breast cancer, Immunotherapy, PARP inhibitors, AKT inhibitors, Sacituzumab Govitecan, Androgen receptor

Introduction

Breast cancer is a leading cause of cancer-related death and the most commonly diagnosed cancer in women worldwide. Triple negative breast cancer (TNBC) is characterised by the lack of the expression progesterone receptor (PR), estrogen receptor (ER) and human epidermal growth factor receptor 2 (HER2), it accounts for between 15% to 20% of all breast cancer. There is a tendency for TNBC to present in younger, premenopausal women and carries a poor prognosis; early relapse and metastatic spread is common in TNBC, with common sites including liver, lungs and brain.

Metastatic TNBC (mTNBC) carries a poorer prognosis when compared with other subtypes of breast cancer. Taxane or anthracycline combinations are classically the first-line systemic treatment options. There is a need for improvement in the management of those with mTNBC, be it novel therapies or altering current regimens to improve survival.

The objective of this paper is to review recent literature on the advancement of the treatment of TNBC in the past 5 years. For the purpose of this review, I focused on five different avenues of advancements in the treatment of TNBC: PD-L1 inhibitors, PARP inhibitors, AKT inhibitors, Sacituzumab govitecan and androgen receptor (AR) inhibitors.

Methodology

A literature search was conducted for clinical trials using PubMed, Embase and Medline. The keywords in the search strategy include: 'triple-negative', 'breast cancer', 'PD-L1 inhibitor', 'PARP inhibitor', 'AKT inhibitor', 'Sacituzumab govitecan', and 'androgen receptor inhibitor'. Articles containing the Medical Subject Headings (MeSH) terms: "Triple Negative Breast Neoplasms/therapy"[MAJR] were retrieved.

The inclusion criteria utilised in this literature review incorporated clinical trials published from January 1st, 2015 to August 21st, 2020. Studies excluded were those with incomplete data on treatment and ER/PR/HER2 status, irrelevant topics i.e., those without the five core areas of interest in this paper: PD-L1 inhibitors, PARP inhibitors, AKT inhibitors, androgen receptor inhibitors, and Sacituzumab Govitecan; and papers reporting the same results, but just one particular population within that study.

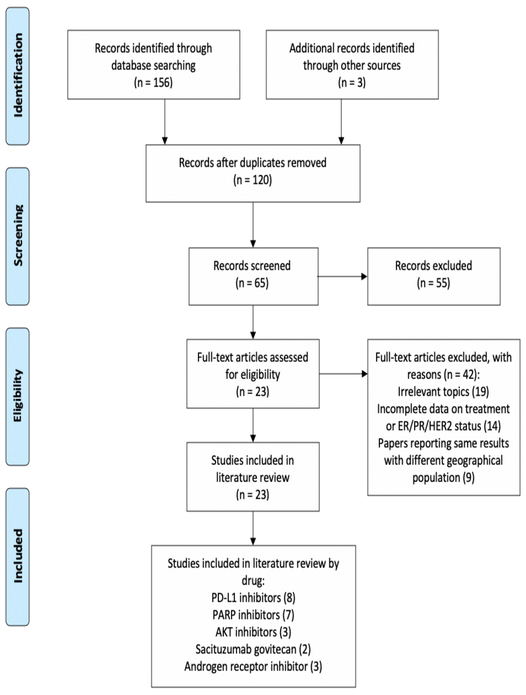

Figure 1. PRISMA diagram showing method of literature search

Findings

PDL1 inhibitors

Pembrolizumab monotherapy showed there was durable antitumor activity in this population, with objective response rate (ORR) of 5.3% and median overall survival (OS) of 18 months[1]. The JAVELIN study showed tumour shrinkage occurred in 45.7% of the TNBC group; disease control rate (DCR) of 31% TNBC[2]. The results from the second interim analysis of the Impassion130 trial showed there was increase in median OS in the atezolizumab group with 21.0 months vs. 18.7 months with the placebo[3]. In the subgroup with PD-L1 immune cell positive tumours, there was a greater increase in the median OS with atezolizumab was 25 months vs. 18 months with placebo[3].

PARP Inhibitors

Metastatic TNBC & BRCA trials included OlympiAD and EMBRACA trials. The OlympiAD trial showed median progression-free survival (PFS) in the olaparib group was 7.0 months compared with 4.2 months in the control group[4-5] and OS in the treatment group was 19.3 vs. 19.6 months. The EMBRACA trial showed significant increase in PFS 8.6 months compared to 5.6 months. In the adjuvant & neoadjuvant setting studies found: the I-SPY2 trial showed veliparib with carboplatin resulted in higher rates of pathological clearance of 51%[7]. The BrighTNess trial showed improved pathological complete response compared to paclitaxel alone (53% vs. 31%)[8]

AKT Inhibitors

The LOTUS trial was the first trial to support AKT inhibitors in mTNBC. median PFS in the was 6.2 months in the Ipatasertib group vs. 4.9 months in the placebo group[9]. The FAIRLANE study showed that there was no evidence that this regime was of clinical or statistical benefit in pCR rate[10]. The PAKT trial showed median PFS was 5.9 months vs. 4.2 months in the control group and median OS was increased 19.1 months, versus 12.6 months in the placebo group[11]

Sacituzumab Govitecan

Results showed objective response rate (ORR) of 30%; median PFS 6 months; and median overall survival was 16.6 months[12]. The 2019 follow up trial showed response rate (3 complete and 33 partial responses) was 33.3% and clinical benefit rate 45.4% and median PFS was 5.5 months, and overall survival was 13.0 months[13]. The ASCENT trial was ceased early by an independent Data Safety Monitoring committee due to the compelling preliminary results of the efficacy in this trial[14].

Androgen Receptor Inhibitors

The enzalutamide study demonstrated clinical activity in patients with advanced androgen receptor positive TNBC and supports the further research of the use of enzalutamide in advanced TNBC[15]. Seviteronel was designed to determine the safety, tolerability and maximum tolerated dose (MTD) in women with unresectable locally advanced TNBC[16]. Abiraterone acetate study showed 6-month clinical benefit rate was 20% including one complete response[17]. Further studies are in currently underway based off these initial results.

Conclusion

TNBC is a disease that has been difficult to treat, with a poor prognosis. Treatment options were limited in both the early and advanced setting to systemic chemotherapy. Now after many years, there are multiple novel therapies with various regimens approved for use in various settings of the disease, with many more showing promise.

Research has shown that there are certain subpopulations that they may be more effective in. PD-L1 inhibitors have been shown to be effective in the metastatic setting, particularly in those with PD-L1 positive tumours. PARP inhibitors have shown to be efficacious in those with BRCA mutations in metastatic TNBC. PD-L1 inhibitors, PARP inhibitors and Sacituzumab govitecan are approved for use by the FDA for the treatment of TNBC in various settings.

Studies showing early promise that are currently under investigations in various trials include those of AKT inhibitors, Sacituzumab govitecan and androgen receptor inhibitors. For the design of future trials careful consideration is necessary to further elucidate research questions including monotherapy versus combination with conventional chemotherapy, their role as maintenance therapy, and the efficacy of one versus another.

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