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Repurposing drugs for Triple negative Breast cancer: dupe of High-end Chemotherapeutics

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Abstract

One of the most prevalent types of cancer is breast cancer. It is commonly occurring type of cancer that can account for nearly 11% of all cancer cases. Breast cancer is further classified into several categories on the basis of histology or molecular subtypes. Molecular subtypes of breast cancer include 'Triple-Negative Breast Cancer' (TNBC). The most severe type of breast cancer, triple-negative breast cancer (TNBC) has a significant recurrence, metastasis and mortality rate. Oestrogen receptors (ERs), progesterone receptors (PRs) and human epidermal growth factor receptors type 2 (HER2s) are all negatively expressed by TNBC. Existing treatments that are generally deployed includes chemotherapy, immunotherapy, radiotherapy and surgery. Along with major side effects the limitations of these therapies are- lack of therapeutic target, chemoresistance and poor prognosis. This review will focus on commonly incorporated conventional treatments and challenges faced. It will highlight the cost effective and novel perspective of drug repurposing. Along with this it will also summarise the futuristic approach of drug repurposing with exclusive examples of repurposed drug for the treatment of TNBC. The generally repurposed drugs are antidiabetic, beta-blockers, NSAIDs.

Key words : TNBC, drug repurposing, drug repositioning, triple-negative breast cancer.

Breast cancer is a pathologic condition in which uncontrolled cell mutation is observed giving rise to tumours in breast. According to WHO reports, breast cancer is one of the most frequent kinds of cancer, followed by skin cancer. It represents over 12% of newly diagnosed instances of cancer. This number goes up to 30% when considered cancer cases diagnosed in women only.[1] Thus, breast cancer ranks as the most frequently diagnosed cancer in U.S. women.

Subtypes of breast cancer can be distinguished by molecular taxonomy or histology. Breast cancer has four main

molecular subgroups.[2] The hormone receptor and/or protein involved plays a major role in defining them.

1. HR+ve /HER2-ve also known as Luminal A
2. HR+ve/HER2+ve also known as Luminal B
3. HR-ve/HER2-ve also known as Triple Negative Breast Cancer
4. HER2 positive

'HR negative or HER2 negative breast cancer' is the other name of triple-negative breast cancer. TNBC is rare and often misunderstood, diagnosed by mammogram. With faster rate of tumour growth TNBC is recognised as highly aggressive type of cancer along with higher chances of recurrence.[3] As the name suggests, it does not express any of the progesterone-receptors (PRs), oestrogen receptors (ERs) or human epidermal growth factor-receptors type 2 (HERs2).[4] This makes the treatment more complicated as negative expression of all the three receptors cut downs hormone therapy and other drug treatments, leaving only chemotherapy in the hands of oncologists. Generally, lumpectomy- removal of tumour or mastectomy- removal of entire breast followed by chemotherapy is the most commonly practiced treatment for TNBC. Although the chemotherapy eradicates the cancerous cells and improves survival of the patients, there's still risk of recurrence and the side effects are quite adverse and may be more damaging to healthy parts of the body.

Present methods of diagnosis and management of TNBC :

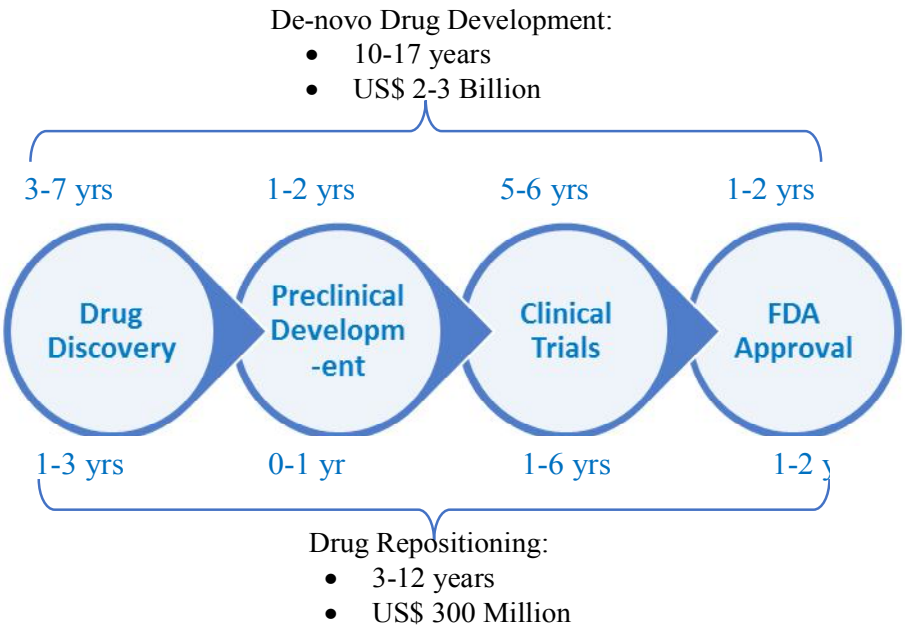
These days, the only FDA-approved treatment TNBC that is non-metastatic is chemotherapy, it additionally comprises platinum, alkylating medications, anthracyclines, microtubule inhibitors and antimetabolites.[5] Also, surgery can be considered. The combination of anthracyclines and taxane agents[3] form the basis of the current standard of care. Even if tumours are initially chemosensitive and different medication combinations are used to intensify therapies, subsequent chemoresistance is often acquired and is associated with a high concentration of cancer stem cells. Since these medications have been approved for uses other than TNBC in the past, they are all repurposed medicines.

Drug Repurposing :

Drug repurposing is commonly called as drug repositioning. Drug repurposing refers to make use of already clinically approved drugs for other indications in the treatment of cancer. It has been emerged as a cost-effective approach for cancer therapy.

The process of finding and developing a novel drug takes a long time and huge financial outlays; it should require ten to seventeen years and amount to two to three billion dollars.[6]

It also includes high chances of failure during clinical investigations, with about 90% of the treatments failed due to unanticipated characteristics.[7] The long costly procedure of new drug discovery and approval can be eradicated by drug repurposing. Also, the drug resistance developed in the oncology therapy by anti-neoplastic agents provide further scope to drug repurposing.[8] At present some of the promising repurposing drugs belongs to beta blockers, NSAIDs, antidiabetics, cardiovascular class of drugs.



1. Drug repositioning Vs conventional drug development

Drug repurposing can be done by using various computational and analytical approaches. These computational approaches are-

1. Data mining-based Drug Repositioning
2. Biological networks-based Drug Repositioning
3. Structural-based Drug Repositioning
4. Transcriptional signature-based drug repositioning.[9,10]

Using these approaches, in-silico drug selection is done. Further process of pre-clinical, clinical development and FDA approval remains same as novel drug discovery.

Drug Repositioning for TNBC :

Treatment of TNBC is quite challenging. The pathogenesis of TNBC reveals that it does not express any of the three hormone receptors (PRs), (HERs2) or (ERs). Thus, drugs acting on this receptors, *i.e.* hormonal therapy cannot be employed in the treatment. Risk of recurrence and adverse side effects are the general drawbacks of conventional chemotherapy. Owing to these challenges, newer approaches of treatment have been studied.

Drug repurposing has been quite interesting approach in the management of TNBC. Following are some highlighted studies of repurposed drugs in TNBC-

1. β *Blockers :*

Subclassifications of β-adrenergic receptors include β1, β2, and β 3. The stress response of the sympathetic nervous system is regulated in many tissues by the process of β1- and β2-ADR activation, which raises levels of intracellular cAMP, in contrast to α2ADR.[11]

Powe *et al*.[12] conducted the first observational study, wherein patients with breast cancer were split into 3 groups: a control group consisting patients without hypertension (n = 374), patients of hypertension treated with β-blockers (n = 43) or other antihypertensive medications (n = 49) before the diagnosis of cancer. The majority of those using β-blockers had selective blockers (7 with bisoprolol and 25 with atenolol); nevertheless, some had non-selective beta blockers (7 propranolol and 4 timolol). The group of people who use β-blockers indicated a markedly decreased chance of developing metastases, tumour recurrence, and mortality from breast cancer. However, additional research was required to compare the effectiveness of selective β1-blockers vs non-selective β1/β2-blockers in TNBC due to patient disparities in the β-ADR antagonists they utilised and the absence of data regarding their type of cancer.

Additionally, Talarico *et al*. (2016) showed that metformin could better minimize metastasis as well as in vivo angiogenesis and in TNBC cells, and that atenolol, a selective β1-blocker suppressed the in vitro proliferation of MDA-MB-435 cells.[13]

More encouraging findings have been published by other research, especially when it comes to recurrence as well as metastasis; the evidence is more robust, if not conclusive, for some cancer subtypes. When beta blockers were administered to 800 women suffering with TNBC, the risk of mortality, metastasis, and recurrence was much lower. Another retrospective population study on breast cancer discovered that, after accounting for variations in disease severity, hypertension, and other variables, beta blockers increased survival without relapse but not overall survival. Beta blockers were linked to a reduced risk of breast cancer metastasis, according to research by Choy *et al*., Powe *et al*. and Parada-Huerta *et al*.[14]

Retrospective investigation by Spera *et al*. revealed an increase in survival without progression, especially for patients with triple negative phenotype and those who did not take beta blockers before receiving cancer therapy.[15]

2. *NSAID's :*

NSAIDs, or non-steroidal anti-inflammatory medicines, are frequently used to treat pain and inflammation. An inhibitory effect of NSAIDs is mostly shown on the enzyme cyclooxygenase (COX). Arachidonic acid cannot be transformed into prostacyclines, thromboxanes or prostaglandins without cyclooxygenase. It is believed that the absence of these eicosanoids is responsible for the therapeutic effects of NSAIDs.[16]

Celecoxib was investigated in 2 trials: the first, a phase II randomised research by conducted by Pierga *et al*.[17] conducted from 2004 to 2007, compared chemotherapy plus celecoxib with chemotherapy alone in 23 females with stage two or three TNBC. Although the researchers claimed that celecoxib failed to increase complete pathological response rates, the paper did not provide a particular comparison of this result for patients with TNBC. The second research included women with primary breast cancer and was a phase II multicenter open-label single arm study conducted by Chow *et al*.[18] Regretfully, the authors were unable to present any data about

this cohort since just 2 primary TNBC patients were included.

Two studies conducted in the past examined aspirin. In their first retrospective investigation, Shiao *et al.*,[19] examined nearly two hundreds of females suffering from stage two or three TNBC in the United States between 2005 and 2013, using data obtained from the TNBC registry of University of Texas Southwestern. Aspirin or clopidogrel was used as anti-platelet therapy for 65 women, whereas no anti-platelet medication was administered to 157 others.

Chemotherapy was not given to a certain proportion of patients in either arm (6.3% and 7.1%, respectively). The first arm showed a significant improvement in both the five-year disease free survival and the five-year distant metastasis hazard ratios (anti-platelet 80.4%, no anti-platelet 62.3%, HR: 0.503 (0.261–0.970); p = 0.04; anti-platelet 8.8%, no anti-platelet 31.9%, HR: 0.310 (0.132–0.729); p = 0.007, respectively). Lastly, Retsky *et al*.[20] presented the revised findings of a retrospective study conducted in Belgium between 2003 and 2008 utilising medical data, in which women who had axillary dissection mastectomy were randomised to receive ketorolac + chemotherapy versus chemotherapy alone. There was no information provided regarding the cohort, including age, the number of patients with TNBC, etc. Additionally, the group getting ketorolac + chemotherapy demonstrated a "far superior disease-free survival in the first few years after surgery," according to the authors' results; however, no specific data regarding TNBC were provided.

3. *Statins :*

Shaitelman *et al*.'s retrospective study examined whether females in stages 1–3 TNBC were taking statins at any point after diagnosis using data from the MD Anderson Cancer Centre. In comparison to the group of non-statin users, the authors demonstrated that patients taking statins had no advantage (0.82 (0.57–1.16); 0.70 (0.47–1.03) relative recurrence chances and mortalities due to breast cancer, respectively); however, when a multivariate analysis was conducted (considering stage, chemotherapy, and levels of cholesterol and triglycerides), the authors found that the use of statin use was anticipated to overall survival (HR: 0.10, p = 0.026, 95% CI: 0.01–0.76).[21]

In a retrospective study conducted between 1995 and 2011, Lacerda *et al*., studied the incidence of loco-regional recurrence in individuals with inflammatory breast cancer who received adjuvant post-mastectomy radiation therapy three years after starting statins. The study used the Breast Cancer Management database at MD Anderson Cancer Centre in the USA. 86 people (102 individuals) had post-mastectomy radiation, and 16 patients had post-mastectomy radiotherapy with statins. Regretfully, there was no information provided on the results in TNBC patients.[22]

4. *Metformin :*

Bayraktar *et. al*.[23] studies metformin in the treatment of TNBC using 3 clinical arms.

I arm- Diabetic patients were given metformin

along with chemotherapy consisiting anthracycline with or without taxane,

II arm- Diabetic patients were given only chemotherapy. Adjuvant chemotherapy consisting of anthracycline with or without taxane,

III arm- It consisted non diabetic patients.

According to their research, metformin administration during adjuvant chemotherapy has no discernible effect on the survival rates of diabetic individuals with triple negative breast cancer.

But metformin proved to reduce chances of recurrence. Overall, 44% recurrences were observed of which 38% were in group of patients taking metformin, 43% in group of patients not taking metformin and 45% in group of non-diabetic patients.

HER2neu-positive breast cancer and localised TNBC are the subjects of a different prospective phase 2 open label randomised controlled trial conducted by Mcbeth[24], which is examining met with neoadjuvant chemotherapy. This is a parallel, randomised, investigator-initiated group superiority experiment. It consists of 2 arms-

I arm- Neoadjuvant chemotherapy along with metformin (850mg twice daily).

II arm- Neoadjuvant chemotherapy without metformin till the surgery.

Numerous repurposed medications and phytochemicals that target distinct signalling pathways cause TNBC cells to undergo cytotoxic activity, which in turn causes cell death, reduces the incidence of recurrence, and halts the metastatic process. In conclusion Different levels of inhibitory effects are seen, and these findings give researchers information and evidence about the medication development process. As a result, further studies and research are required to obtain more effective therapeutic treatment alternatives for TNBC.

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