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Repositioning of FDA Approved Drugs in Breast Cancer

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ABSTRACT:

Medication repositioning and therapeutic switching are other names for drug repurposing. This technique is utilised to separate the innovative therapeutic agents from the FDA-approved medicinal compounds currently being employed in clinical trials. It is regarded as an effective method for creating drug candidates with novel therapeutic or pharmacological features. The unique strategy of drug repositioning is used to boost the success rate of medication development because drug discovery is an expensive, time-consuming, arduous, and extremely risky procedure. This approach has many advantages over the conventional drug discovery procedure, including a shorter drug development timeline, lower costs, higher efficiency, and a lower risk of failure. Breast cancer, which has a high mortality rate, is the most common type of cancer among women globally. One of the biggest obstacles to be overcome in the treatment of breast cancer, medication resistance, is mostly to blame for this high mortality rate. As a result, research has been concentrated on discovering novel therapeutic tools, particularly those that permit a tailored treatment based on patients' features. In spite of the scientific community's concern for ensuring the quality of life for cancer patients, researchers are also conscious of the rising expenses associated with cancer therapy, and efforts have been made to find alternatives to the development of new drugs. The multistep, expensive, and time-consuming process of developing new medications has several drawbacks. It involves clinical studies, many of which are unsuccessful in the early

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stages. Drug repurposing is a method for overcoming these drawbacks. In this research, we described prospective medications for the treatment of breast cancer while taking into account their pharmaco-genomic profile to evaluate the correlation between a patient's genetic makeup and the treatment they get. This review argues in favour of the necessity of conducting additional basic research in this field in order to examine and advance our understanding of the existing and prospective future treatments for breast cancer.

Keywords: repurposed drugs; anticancer drugs; cancer drug resistance; pharmacology; therapeutic strategies.

INTRODUCTION:

Cancer is remains one of the major causes of mortality globally, despite the enormous efforts that have been made over the years to develop cancer therapies. This disease is one of the main causes of worry for world health because of its high incidence and fatality rates [1]. Despite the fact that there are many therapeutic approaches available to treat this condition, the current therapy plans are frequently accompanied by the development of drug resistance by the tumour cells, which lowers the antitumor efficacy of the therapeutic agents. This illustrates the pressing necessity for the creation of fresh treatments or new anti-cancer medications to combat this problem [2-4]. However, the process of creating new medications is a very costly one that takes several steps, including the design and manufacture of the medicine as well as repeated testing of its safety and effectiveness in animal models. It is also necessary to do additional clinical research to confirm.

REPURPOSING MEDICINE:

A NEW SCREEN FOR CANCER TREATMENT

Drug repositioning, another name for medicine repurposing, is a tactic that investigates other ailments for which a drug that has already received approval can be used. It has been suggested by a number of authors as an alternative method to improve the number of therapeutic tools available for the treatment of cancer and offers numerous advantages over the development of new cancer drugs. Because the drug's pharmacokinetic and pharmacodynamic profiles have previously been fully described, there is no need for extensive research, which speeds up the translational process and reduces associated costs, making the procedure a big success [2, 5, 7]. These days, according to Koushik and colleagues, this strategy involves some crucial steps that researchers must carry out in order to determine the repurposing potential of a particular drug. These steps include not only pre-clinical approaches like in silico, in vitro, or in vivo studies but also clinical observations and epidemiological studies [18-20]. As a result, it is possible to locate viable candidates for drug repurposing for anti-cancer therapy by identifying a medicine's anti-neoplastic effects and researching its targeted biochemical pathways. A repurposed medicine frequently has unidentified molecular pathways that interact with any pathway implicated in the cancer

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hallmarks Hanahan described in 2000 (updated in 2021), the so-called "off-target" impacts of the therapeutic drugs, which might produce unanticipated anti-tumor effects [20-22]. Examining how their modification of the gene expression linked to a certain cancer profile is related to another method of identifying viable candidates for medication repurposing. Drugs that can affect a gene's expression can be helpful for oncology treatment because some cancer types can occasionally have up- or down-regulated genes [22,23].

DRUG RE-POSITIONING CHALLENGES:

Drug repurposing therapy has its share of difficulties as well [23]. Drugs that have been repurposed can be used alone, as chemo-preventive agents, or to complement the effects of other chemotherapeutics. Additionally, they can be used as an adjuvant therapy to prevent tumour recurrence or to manage the side effects of other medications. They can be coupled with other medications to focus on other oncogenic pathways or to work in concert to completely eradicate the tumour. Drug resistance is more likely to develop when they are used as monotherapies [24, 25]. Since each of the therapeutic drugs can work through different pathways and intensify the overall anti-tumor action, medication combinations are typically more effective than monotherapy [2, 18]. However, despite the greater anticancer effects, a multiple therapy plan can lead to more undesirable side effects from drug-drug interactions, which can make the treatment less effective [26]. Because of genetic variations across patients, the manner in which a drug is absorbed, digested, distributed, and expelled (pharmacokinetics), as well as the role of the drug in the body (pharmacodynamics), might vary between patients and affect how a drug therapy works [28,29]. As a result, pharmaco-genetics, a precision medicine technique that enables the prediction of the response to a treatment scheme based on certain genetic indicators, must be taken into account when treating a patient with a given drug. This method aids in determining whether the medicine is harmful to tumours or whether the patient has polymorphisms that could result in unanticipated side effects [28,30]. Therefore, it is crucial to carry out comprehensive genomic studies that aid in creating a mutational profile of the patients, allowing individuals to be categorized based on their molecular characteristics. Based on the genetic makeup of the patients, this will aid in choosing the proper therapy regimens [29, 31].

REPURPOSED DRUGS IN BREAST CANCER TREATMENT:

BIOMARKERS ASSOCIATED WITH DIFFERENT OUTCOMES

To the greatest of our knowledge, these medications have been repurposed and are associated with the majority of pertinent data regarding their impact on patient genetic variants. They must be the subject of future studies, incorporating a larger number of breast cancer patients and stratification groups depending on their genetic profile, as they are further discussed in the paragraphs that follow. Doxorubicin is a member of the anthracycline class of antibiotics, a subclass that was formerly isolated from the bacterium Streptomyces peucetius. It was

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given medical approval in 1974, but it wasn't until 20 years later that its importance for treating breast cancer was made clear [31,32]. Its mode of action involves DNA intercalation, which results in DNA strand breaks, and impairment of topoisomerase-II-mediated DNA repair, which prevents DNA repair replication mechanism. Despite the fact that this medication has a patient-dependent tumour response and is linked to significant toxicity, it is frequently employed as a chemotherapeutic agent in the treatment of breast cancer and other malignancies [29–32]. Given that various studies demonstrate that the level of toxicity is influenced by the genetic variability of the patients, cardio-toxicity is in fact one of the most crucial factors to take into account when administering doxorubicin [31,32,34,35]. Doxorubicin acts as a substrate for protein importers in both breast tissues and cardiac muscle, which may explain why it causes cardiotoxicity [34,36]. Single nucleotide polymorphisms (SNPs) in the human leukocyte antigen (HLA) region were studied by Todorova and colleagues, who claimed that these polymorphisms may put people at risk for doxorubicin-mediated cardiotoxicity and immunological and inflammatory dysregulation [31,34]. Additionally, according to previous research, cytokine profile analysis is required in order to be employed as a biomarker to evaluate patients' cardio-sensitivity prior to doxorubicin treatment [37].

Immunological response. In the tumour microenvironment, it reduces the suppressive regulatory T cells and increases the effector T cells [31]. This medication is being used to treat breast cancer and other cancers. Depending on the amount, this substance performs a variety of various tasks: at lower concentrations, it affects immunological function; at greater concentrations, it serves as an alkylating agent, resulting in cancer and lymphoid cell death [40]. The bioactivation of this chemotherapy drug is dependent on cytochrome P450 (CYP) enzymes. Several genes, particularly the well-known CYP2B6 and CYP2C19, encode these enzymes to be polymorphic. Understanding the functions of various variations of these genes in the response to therapy requires additional in-depth research, as some of these genetic variants may result in function alteration or even deletion. According to certain studies, the genetic polymorphisms in the CYP2C19 (rs4244285, *1/*17/*2) and CYP2B6 (rs12721655, rs3745274, *1, *6) genes have an impact on the drug's bioactivation and are therefore associated to the effectiveness of cyclophosphamide treatment for breast cancer [41,42]. These findings suggest that cancer patients should undergo genotyping for these gene SNPs before receiving cyclophosphamide since these polymorphisms are connected to the metabolic conversion of the medication into its bioactive form. Tamoxifen, an oestrogen receptor selective modulator, was initially developed for the Albright syndrome, as well as to induce ovulation [29,31]. It can bind to oestrogen receptors and exhibit anti-neoplastic properties in the breast tissue as a competitive inhibitor of estradiol. Tamoxifen was first suggested as an adjuvant therapy for hormone receptor-positive breast cancer for this reason many years ago [42,47]. Tamoxifen's unfavourable effects on the liver and tumour resistance to the drug's therapy are the main challenges while taking it [41,48]. The pharmacologic causes shown in Figure 2 could be the cause of the drug resistance mechanisms: The

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cytochrome P450 family of genes, notably CYP2D6, which has a wide range of genetic variants connected with it, convert tamoxifen into its major active form, endoxifen [47]. Numerous studies have been created to evaluate the impact of the genetic variations of CYP2D6 in tumor resistance. Due to inconsistent results, there is currently no definite association [49–51]. To connect the genotyping of this gene with the outcomes of the disease, it is necessary to clarify the association between SNPs in CYP2D6 and the mechanisms of drug resistance and the side effects seen with the treatment with tamoxifen [48]. The rate at which tamoxifen is metabolised has recently been shown to be clearly correlated with SNPs in the CYP2D6 gene. This reinforces the significance of genotyping this gene to enable dosage adjustments for medications to improve therapeutic effectiveness or, in the case of patients with poor metabolizers, to indicate that the drug in question is insufficient and that a different medication should be used [42]. The rs4646 SNP of CYP19A1 has also been linked, according to this study with the effectiveness of tamoxifen.

The Albright syndrome and ovulation induction were two of tamoxifen's original uses as a selective oestrogen receptor modulator [29,31]. It can bind to oestrogen receptors as a competitive inhibitor of estradiol and exhibit anti-neoplastic properties in the mammary tissue. For this reason, tamoxifen was first suggested as an adjuvant therapy for hormone receptor-positive breast cancer several decades ago [42,47]. Tamoxifen's unfavourable effects on the liver and tumour resistance to the medication present the most challenges [41,48]. Pharmacologic factors, as shown in Figure 2, may be responsible for the processes of drug resistance. The cytochrome P450 family of genes, notably CYP2D6, which has a role in converting tamoxifen into its primary active form, endoxifen, play this role myriad of genetic polymorphisms associated with it [47]. Numerous research have been conducted to evaluate the role of CYP2D6 genetic variations in tumour resistance. Due to inconsistent results, there hasn't been a definitive association as of yet [49–51]. To connect the genotyping of this gene with the outcomes of the disease, it is necessary to clarify the relationship between SNPs in CYP2D6 and the mechanisms of drug resistance and adverse effects seen with the use of tamoxifen [48]. Recently, a strong correlation between CYP2D6 SNPs and the rate at which tamoxifen is metabolised was discovered. This confirms the significance of genotyping this gene to enable drug dose adjustments to improve the efficacy of therapy, or in the case of individuals with poor metabolizers, suggests that this drug is not appropriate for them adequate and another one must be selected [42]. Additionally, this study also describes rs4646 SNP of CYP19A1 as being associated with the effectiveness of tamoxifen.

Another medicine that was originally intended to treat arterial restenosis is paclitaxel. In 1971, it was separated from pacific yew for the first time. It was originally applied to cancer in 1992, specifically ovarian cancer [31]. Currently, paclitaxel is used to treat ovarian and breast cancer as an adjuvant or neoadjuvant therapy. Its anti-tumor strategy involves preventing cells from going through mitosis, which reduces the rate at which cancer cells proliferate [29,31]. The genetic variability of the patients is largely responsible for the

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dispersion in the tumour response rate to paclitaxel. Some SNPs on LPHN2, ROBO1, SNTG1, and GRIK1 have been identified in in silico studies as potential predictive biomarkers of tumour insensitivity to paclitaxel. These findings are currently being investigated at the moment.

DISCUSSION OF THE FUTURE DIRECTIONS IN CANCER TREATMENT CONCERNING DRUG REPURPOSING:

The creation of more precise cancer therapies in medicine has been made possible by the discovery of new biotechnological weapons that take into account the genetic makeup of the patients and advancements in medication repurposing, a potent technique for the discovery of new cancer therapies. With the goal of rationally designing treatment regimens based on the patient's characteristics, precision medicine has enormous promise and is a study field that is still in its infancy [59, 60]. In order to do this, it is crucial to concentrate on the medications' mode of action as well as the molecular targets that may support their anticancer impact. Among the most crucial target cells in the treatment of breast carcinoma is cancer stem cells (CSCs). These cells play a role in the formation, metastasis, and recurrence of tumours as well as the emergence of defence mechanisms against various therapeutic modalities.

Treating the cancer landscape using combinatory treatment models that provide a multi-target effect is the key to solving this issue. Combining traditional anticancer medicines with newly developed medications may improve therapeutic efficacy, but this approach occasionally involves drug-drug interactions that may have unexpected effects and should be carefully considered before developing combination therapy [62]. On the other hand, carefully planned combination therapy can be a potent pharmacological strategy to address the genetic variability across cancer patients [63]. Indeed, Law [64] and Frei [65] proposed the rational design of medication combinations a number of years ago, presuming that cancer cells within the same tumour (intratumoral heterogeneity) that are resistant to one therapy can be destroyed by a second, distinct drug (and vice versa). In fact, additional research has shown that this is also applicable for the heterogeneity across patients, and patients whose cancer did not respond to one treatment option had a probability of reacting to a second, unrelated treatment option [65–67].

Combination therapies have been shown to be more effective than monotherapies in the treatment of several cancer types [68–74], but few studies have linked the genetic make-up of tumour cells to the effects of the medications, particularly when researching repurposed pharmaceuticals. Few studies have attempted to explain the genetic underpinnings behind repurposed medications' mode of action, even when used in monotherapies. The majority of the mechanisms investigated when researching repurposed medications are based on fundamental carcinogenesis signalling pathways like PI3K-AKT-mTOR and focus on DNA damage, apoptosis, or the expression of significant cancer-related proteins like p53 or Bcl-2 [75-79]. The most recent research by Kumari et al., which utilised transcriptional analysis to

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comprehend the genes involved in artemisin anti-migratory and reduced invasive effects. A well-known antimalarial medication called artemisin has been shown to have strong anticancer effects on several cancers [80]. Studies like this allow us to understand if there is an up- or down regulation of important genes, such as tumor suppressor genes or oncogenes associated with growth stimulating signaling pathways and relate these changes with the genetic predisposition of cancer patients.

The meticulous design of clinical trials—more precisely, the study design—must scrutinise the various groups of cancer patients based on their genetic profiles, allowing classification based on the predictive response to a specific medicine to provide more suitable treatments and drug dose administration to each patient group. This is a crucial step in enhancing the possibility for translation of repurposed drugs into clinics. Additionally, it's crucial to provide these cancer patients the appropriate follow-up, modify dosages as needed, and gain a deeper understanding of the advantages and downsides of the treatment, as this could be the secret to "speeding up" the translational potential [25, 59].

CONCLUSION AND DSR'S FUTURE PERSPECTIVE:

In light of the usage of repurposed pharmaceuticals and their benefits, this review's conclusion underlines the current advancements made in the field of personalized cancer treatment based on patient tumour heterogeneity. One of the major causes of death worldwide, cancer has various negative health and financial effects. The development of anticancer drug resistance mechanisms by tumour cells is one of the challenges facing the treatment of cancer, which lowers the therapeutic efficacy of the current therapies. This demonstrates the pressing need for the creation of innovative treatments or medications for cancer. Compared to de novo development, drug repurposing is a cost-effective, time-saving method for increasing the number of clinically available cancer treatments. It also plays a significant role in the formulation of more individualized treatment plans. Due of the heterogeneity of cancer, precision medicine is currently a prominent topic in the field of cancer treatment. In this post, we covered how patient genetic differences may be able to forecast various results or even foresee potential harmful occurrences in reaction to a certain treatment. Our results confirm the need for immediate research into the pharmacokinetics and pharmacodynamics of the existing medications in relation to each patient's unique tumour genetic profile, as well as the identification of new biomarkers that may serve as prospective targets for treatment.

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