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Review article

Drug combination and repurposing for cancer therapy: the example of breast cancer

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ABSTRACT

Cancer is a set of extremely complex diseases, which are increasingly prominent today, as it affects and kills millions of people worldwide, being the subject of intense study both in its pathophysiology and therapy. Especially in women, breast cancer is still a cancer with a high incidence and mortality. Even though mortality rates for this type of cancer have declined in recent years, it remains challenging at the treatment level, especially the metastatic type. Due to all the impact on health, cancer therapy is the subject of costly and intense research. To enrich this therapy, as well as decrease its underlying high associated costs, drug repurposing and drug combinations are strategies that have been increasingly studied and addressed. As the name implies, drug repurposing presupposes giving new purposes to agents which, in this case, are approved for the therapy of other diseases (for example, cardiovascular or metabolic diseases), but are not approved for cancer therapy. Therefore, a better knowledge of these therapeutic modalities for breast cancer therapy is crucial for improved therapy. In this particular review, we will discuss some relevant aspects of cancer and, particularly, breast cancer and its therapy. Also, drug combination and repurposing will be highlighted, together with relevant examples. Despite some limitations that need to be overcome, these methodologies are extremely important and advantageous in combating several current problems of cancer therapy, namely in terms of costs and resistance to current therapeutic modalities. These approaches will be explored with a special focus on breast cancer.

1. Introduction

Cancer, also called malignant neoplasm is a deviation from the coordinated interaction among cells and organs [1]. It is a complex group of diseases involving abnormal cell growth, in which there is a potential to invade and/or spread to other body tissues [2]. This is the second most common form of death from illness [1], accounting for an amount of 9.6 million deaths in the year of 2018 [3]. Nearly half of all these cancer deaths are due to liver, lung, stomach, and bowel cancers, although the most frequent cancers worldwide are lung and bowel, but also female breast and prostate cancers. Particularly, these four cancer types account for around 4 in 10 of all cancers diagnosed in the whole world [4]. Despite the high impact on human health, the economic impact of cancer is also very relevant and is increasing throughout the years. As an example, in 2020, the total economic cost of cancer is estimated to exceed €100 billion [4, 5]. Thus, approaches to fight against this problem are of extreme importance because an investment is needed to ensure long-term strategies of prevention and therapies [5, 6].

2. Main text

2.1. Cancer treatment modalities and its difficulties

When dealing with cancer, it is important to follow the following scheme: prevention, early detection, and total eradication. However, these three measures are, in the great majority of the times, difficult to achieve, being a complex issue. Thus, the necessity of the need for personalized, individualized, treatment is imperative [7]. Three usual modes exist: surgery (excision of the primary tumor), radiotherapy and pharmacotherapy. The choice of the right anticancer agents, as well as

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the right doses, ways of administration and management of toxicities, is a hard and extremely complex process. In this regard, a healthcare team very with very expertise in the use of all these therapeutic modalities is required. Choosing and verifying options of treatment with a focus on the individual patient and on heterogeneity of this disease is a crucial issue in dealing with the right administration of the diverse anticancer agents, being a hard but very important issue to develop [8].

Regarding pharmacotherapy, it can be said that the gold standard drug is the one that kills selectively the neoplastic cells, reducing the adverse effects. However, neoplastic and normal cells differ, mainly, quantitatively, such as in the degree of activation of signaling pathways, sensitivity to hormones or growth factors and different growth parameters. Thus, cancer pharmacotherapy is hard to achieve [9]. Nevertheless, survival of patients with this condition increased recently, mainly due to upgraded therapies (such as better chemotherapeutic drugs and targeted therapies), multidisciplinary and personalized care, and improved palliative care services [10]. However, despite the advances, there is still a lot of therapy failure, that can be explained by varied drug resistance mechanisms, intra and intertumoral heterogeneity and inherent complexity of this group of diseases [11]. Pharmacological research in oncology is being intensively made, leading to a strong increase in the costs of new therapeutic agents. The problem in this situation is the fact that there is an increasing recognition that most national healthcare services won't be able to stand these costs [12]. Despite this astronomic investment, there is little output that does not follow the big spending and research. This gap in productivity remains even though the investment of astronomic amounts of money in novel discovery technologies. So, there is an extreme need for creativity to find new uses and improved versions of existing drugs [13]. In fact, cancer care cost increased, respectively, about 19%, 31% and 28% in the initial, continuing and the last phase of care in 2020, compared with data from 2010 [14].

Another problem in oncologic research is the fact that cancer is a very complex disease, in which exists distinct molecular patterns with different levels of sensitivity to the different treatments, leading to resistance to the different therapeutic modalities [15, 16]. Thus, more effective cancer agents are required. To solve this issue, an approach called drug repurposing, is being extensively studied and applied [17]. To highlight the important role of this methodology, the global market associated with this approach reached €20.7 billion in 2015 and €31 billion by the year of 2020 [18]. Besides, another relevant response to the many above mentioned problems in oncological therapy, includes the use of drug combination therapy [19]. Both these methodologies will be discussed further in this review.

2.2. Breast cancer

Breast cancer is the second most frequent type of cancer in the world and the fifth most common cause of death from cancer. Although it is still the most frequent cause of cancer death in women in underdevelopment regions, in more developed countries it is the second most frequent cause of cancer death in women, following lung cancer. Breast cancer not only occurs in women but also occur in men. However, it is a rare condition, less than 1% [20]. In the last two decades, occurred a decline of 30% in the rates of mortality by this cancer, with improvements in 5-year overall survival rates to an order of 90%. However, the metastatic type of breast cancer remains a challenge to treat, despite these signs of progresse. Particularly, in 2020, nearly 2.3 million new cases of breast cancer were identified and more than 600.000 cases of breast cancer-associated death occurred in the world [21]. Thus, a large portion of the global population is affected by this disease, which constitutes an important public health issue. As a consequence, it has generated a lot of research interest [22].

2.2.1. Breast cancer therapeutics

Even though breast cancer is still very prevalent, there is a reduction in mortality over the years, mainly due to improvements in the diagnosis and management, varying widely between diverse geographic areas [23]. However, the treatment of metastatic disease remains a huge challenge, despite advances with a better knowledge of the use of therapies for breast cancer of early stage [24]. In fact, metastasis is the major cause of mortality for breast cancer patients, being the most severe form of the disease, in which a huge genetic complexity is present [25]. Thus, the choices of treatment regimens for breast cancer depend on diverse factors, namely the stage and subtype of cancer, the hormone receptor status, if the cancer is HER2 positive or negative, the overall health status of the person (particularly if the person has some other diseases or not, or some historical of cancer), if the woman has gone through menopause or not and, depending on the tolerability to the therapy, it may be adjusted to other treatment options. Given this complexity, it is hard to have an accepted treatment in an universal way, mainly because each case is unique, and the choice of the best therapeutic regimen should be tailored to everyone. Highly qualified healthcare providers are important to evaluate the best therapy, in a personalized way [26]. The right choice of therapy must consider the benefits over risks. Monitoring the doses, the adherence to therapy, dosing plans and the respective responses to the treatment regimen is a crucial issue [23, 27]. Table 1 lists the main drugs approved by the FDA (Food and Drug Administration) to prevent and treat breast cancer, as well as a brief description of each drug.

2.3. Drug combinations in cancer

A disease can be interpreted as a group of interconnected molecular pathways, having a big susceptibility to the simultaneous action of different drugs. This makes possible to investigate combinations of drugs in greater detail [30]. There are several pros in drug combination: less toxicity, increased efficacy, decreased dosage at an equal or increased level of efficacy and possibility of antagonizing drug resistance in oncological therapy [31]. Due to these mentioned advantages, a combination of drugs represents a very important therapeutic modality that has become extensively used for the treatment of different diseases, such as infectious diseases and different types of cancer [30].

Chemotherapy can be very toxic to the patient, with several adverse effects and risks, reducing instrongly the immunity by affecting the cells of bone marrow and increasing susceptibility to host diseases, non-selectively targeting actively proliferating cells, which leads to the destruction of not only neoplastic but also non-neoplastic cells, resulting in damage to the host and its biological systems [32]. Thus, despite combination therapy can be toxic, this toxicity can, also, be less pronounced due to the fact that different signaling pathways will be targeted. Also, monotherapy is, in general, less effective than the combination therapy modality, although being still a very usual treatment modality. A big advantage underlying combination therapy is the fact that this works in a synergistic form. Therefore, less therapeutic dosages of every single drug is required. Also, combination therapy is capable of producing cytotoxic effects on neoplastic cells while, simultaneously, preventing toxic effects on healthy cells. This occurs if one drug in the combination is antagonistic, in terms of cytotoxicity, to another drug in normal cells [33]. In cancer, a vast number of clinical trials testing different combinations are being carried out, namely chemotherapeutic agents, radiation and hormonal therapies, molecularly targeted therapeutic agents, and immunotherapies [34], with special focus on cytotoxic agents and biotherapies (such as monoclonal or polyclonal antibodies, vaccines, gene therapy, cytokine therapy) combinations [35].

Combining both repurposed and chemotherapetic agents have also shown very interesting results, important when the usual anti-cancer monotherapy has demonstrated failures in the safety and tolerability of oncological patients. Examples of these combinations are nitroglycerin (used routinely for angina pectoris), combined with vinorelbine and cisplatin, and clarithromycin (used to treat bacterial infections) combined with bortezomib, an anticancer drug. In the first example, a phase II randomized trial reported improved survival of patients with non-squamous cell lung cancer. In the case of clarithromycin, it has been

Table 1. Drugs approved by the FDA for breast cancer therapeutics. Adapted from References [28] and [29].

	Drugs approved for breast cancer	Brief description
To Prevent	Raloxifene Hydrochloride	Selective Estrogen Receptor Modulator (SERM). Competes with estrogen for the binding to the estrogen receptor.
	Tamoxifen Citrate	SERM. The active metabolites of this drug compete with estrogen for the binding to the estrogen receptor.
To Treat	Abemaciclib	Cyclin-Dependent Kinase (CDK) inhibitor, that targets the CDK4 and CDK6.
	Alpelisib	Inhibits PI3K in the PI3K/AKT kinase signaling pathway, inhibiting the activation of this signaling pathway
	Anastrozole	Nonsteroidal inhibitor of aromatase, which effectively blocks estrogen synthesis
	Ado-Trastuzumab Emtansine	Monoclonal antibody, trastuzumab, linked to emtansine, a cytotoxic drug. Trastuzumab stops cancer cells growth, binding to the HER2/neu receptor. Emtansine destroys cells by binding to tubulin
	Atezolizumab	Monoclonal antibody directed against programmed death- ligand-1 (PD-L1)
	Capecitabine	Fluorouracil prodrug that is used as an antineoplastic antimetabolite. Inhibits the synthesis of DNA, RNA and proteins, as well as cell division
	Cyclophosphamide	Alkylating agent with both antineoplastic and immunosuppressive activities. Forms DNA crosslinks both between and within DNA strands
	Docetaxel	Antimitotic chemotherapy drug, plant alkaloid. Promotes and stabilizes microtubule assembly
	Doxorubicin Hydrochloride	Hydrochloride salt of doxorubicin, an anthracycline antibiotic. Intercalates between base pairs in DNA, inhibits the enzyme topoisomerase II and forms oxygen free radicals
	Epirubicin Hydrochloride	Hydrochloride salt of the 4′-epi-isomer of doxorubicin. Intercalates between base pairs in DNA, inhibits the enzyme topoisomerase II and forms oxygen free radicals
	Eribulin Mesylate	Binds to tubulin and inhibits the polymerization of tubulin and the assembly of microtubules
	Everolimus	mTOR kinase inhibitor, inhibiting its downstream signaling
	Exemestane	Steroidal aromatase inhibitor. Reduce estrogen levels, blocking the action of aromatase
	5-FU (5-Fluorouracil)	Analog of pyrimidine, being classified as an antimetabolite. Both fluorouracil and its metabolites incorporate into RNA, inhibiting RNA processing. Also, inhibits the synthesis of DNA
	Fulvestrant	Estrogen Receptor antagonist. The results are estrogen receptor deformation and decreased estrogen binding
	Gemcitabine Hydrochloride	Converted intracellularly to its active metabolites, leading to a decrease in the available deoxynucleotide pool for DNA synthesis and incorporation
	Goserelin Acetate	Analog of luteinizing hormone-releasing hormone. Decreases estradiol production.
	Ixabepilone	Binds to tubulin and promotes its polymerization. Promotes microtubule stabilization
	Lapatinib Ditosylate	Blocks phosphorylation of EGFR and Erk-1 and-2 and AKT kinases, inhibiting pathways of cell proliferation and survival
	Letrozole	Nonsteroidal inhibitor of estrogen synthesis. Inhibits aromatase.
	Megestrol Acetate	Derivative of progesterone, with anti-estrogenic and antineoplastic activity
	Methotrexate	Antimetabolite and antifolate drug with anticancer and immunosuppressant activities. Inhibits the synthesis of DNA, RNA and proteins
	Neratinib Maleate	Tyrosine kinase inhibitor that exhibits antitumor action against carcinomas that express EGFR, HER2 and HER4
	Olaparib	Binds and inhibits PARP (Poly (ADP-ribose) Polymerase), inhibiting PARP-mediated repair of DNA breaks
	Paclitaxel	Inhibits the disassembly of microtubules by binding to tubulin, stopping cell division. Also, induces apoptosis by blocking Bcl-2 function (antiapoptotic protein)
	Palbociclib	CDK inhibitor. Inhibits CDK4 and CDK6, inhibiting retinoblastoma protein phosphorylation in the G1 phase of cell cycle

(*continued on next page*)

Table 1 (*continued*)

Drugs approved for breast cancer	Brief description
Pamidronate	Inhibits the enzyme farnesyl pyrophosphate synthase important in the mevalonate pathway
Pembrolizumab	Monoclonal antibody against programmed cell death protein 1 (PD-1) receptor
Pertuzumab	Recombinant monoclonal antibody. Targets the extracellular dimerization domain of HER2
Ribociclib	CDK inhibitor that deregulates cell cycle by targeting cyclin D1/CDK4 and cyclin D3/CDK6 pathway
Sacituzumab	Monoclonal antibody against tumor-associated calcium signal transducer 2
Talazoparib	Inhibitor of the nuclear enzyme poly (ADP-ribose) polymerase.
Tamoxifen Citrate	SERM. The active metabolites of this agent compete with estrogen for binding to the estrogen receptor.
Thiotepa	Alkylating agent that interferes with both DNA replication and cell division
Toremifene	SERM. Binds competitively to estrogen receptors.
Trastuzumab	Monoclonal antibody against the extracellular domain of the HER2 receptor
Tucatinib	Inhibits the human epidermal growth factor receptor tyrosine kinase (HER2 receptor)
Vinblastine Sulfate	Disrupts microtubule function and formation and interferes with the metabolism of glutamic acid

shown to induce apoptosis when combined with bortezomib, being only effective when administered in a combination in myeloma and breast cancer cells. For example, another combination of agents may be composed of a repurposed protector agent and another drug that kills neoplastic cells. In this way, the protector drug may be a repurposed drug shown to also display protection over healthy cells in oncological therapy [33].

In theory, there are a lot of examples of drug combinations that seem to be attractive, based on complementary mechanisms of action that are complementary. Some examples are the combinations of 5-FU/leucovorin/irinotecan (FOLFIRI) and capecitabine/oxaliplatin (CAPOX), used typically in colorectal cancer. The mechanisms of action that contribute to the cytotoxic effect are different for the different drugs, being complementary to promote cell death [36].

However, mainly because of efficacy or safety/tolerability issues, proved to be unsuccessful [37]. A known example is VEGF and EGFR inhibitors (bevacizumab and erlotinib, respectively) that, as single agents, demonstrated anticancer activities. However, when used in combination, the co-inhibition of the two pathways did not demonstrate an improvement in efficacy in patients with non-small-cell lung cancer, despite good results from phase I and phase II studies [38].

Even though notable advantages, many challenges in oncological combination therapies remain. Notably, this kind of therapy remains a little restricted by toxicity to healthy cells. Furthermore, to be effective, molecularly targeted agents and many combinations of these kinds of therapies require a target inhibition in a simultaneous way. Consequently, face problems related to pharmacokinetic and potential toxicity to the healthy tissue [39].

2.3.1. Synergy definition and reference models to detect synergy

When in combination, two agents producing the same broad therapeutic result can produce the same outcome of various magnitudes compared with the summation of the effects of single agents. This effect can be bigger, equal, or less than this respective summation, being synergistic, additive or antagonistic, respectively [40]. Thus, if two or more drugs act synergistically, the possibility of reaching the desired outcome, such as cancer cell death, can be achieved by lower doses of each drug, minimizing their respective adverse effects, associated with higher doses.

The establishment of a reference model to detect and define synergy and antagonism is very important, serving the baseline for quantifying the interaction of two drugs, based on their individual interaction when neither antagonism nor synergy is presented, defined as additivity. Therefore, deviations of this baseline can, then, be synergistic or antagonistic interactions. There are numerous proposed reference models for additive drug interactions, being full of permanent confusions and controversies, as manifested by over 20 definitions of synergy and discrepancies in its determination [41]. In this way, there is still no universally accepted guideline on how to select the ideal reference model [42], and to understand these models, complex mathematical and pharmacological concepts are necessary [30].

Essentially, there are three groups of reference models: Highest Single Agent (HSA) model, Loewe Additivity and Bliss Independence models. They have been built up based on different suppositions about the expected additive outcome of the combination [42]. The HSA model assumes that the expected result of the combination equals the higher single drug effect at the dose in the combination, reflecting that the effect of a combination of agents is greater than the effects produced by its single agents [29, 42]. In its turn, the Loewe additivity model is based on the idea that a drug is mixed with itself, being not expected to exist any interaction once a single drug cannot interact with itself. So, Loewe model defines the expected result (additivity) as if a drug was combined with itself. On the other hand, the Bliss Independence model is based on the idea of non-interaction, that each drug is acting independently of one another, but each contributes to a common result. In this way, additivity can be obtained based on the possibility of independent events [30, 42].

Table 2. Drug combinations approved by FDA to breast cancer therapeutics. Adapted from Reference [42].

Drug Combinations used in Breast Cancer	Brief Description
AC	Chemotherapy regimen composed by Doxorubicin Hydrochloride (Adriamycin) and Cyclophosphamide
AC-T	Chemotherapy regimen composed by Doxorubicin Hydrochloride and Cyclophosphamide, followed by Paclitaxel (Taxol)
CAF	Chemotherapy regimen composed by Cyclophosphamide, Doxorubicin Hydrochloride (Adriamycin), and 5-Fluorouracil
CMF	Chemotherapy regimen composed by Cyclophosphamide, Methotrexate, and 5-Fluorouracil
FEC	Chemotherapy regimen composed by 5-Fluorouracil, Epirubicin and Cyclophosphamide
TAC	Chemotherapy regimen composed by Docetaxel (Taxotere), Doxorubicin Hydrochloride and Cyclophosphamide

2.3.2. Drug combinations in breast cancer

Briefly, it can be stated that there are several breast cancer drug combination regimens that have been shown to be effective, even though there are exceptions and there are also no standard regimens, since breast cancer therapy depends always on numerous factors, as mentioned above. There are six very well characterized drug combinations (Table 2). AC (doxorubicin combined with cyclophosphamide) is used as adjuvant therapy for the primary treatment of breast cancer and for the treatment of metastatic and recurrent breast cancer [43]. This regimen can be followed by paclitaxel (AC-T), also used as an adjuvant treatment for breast cancer [44]. Additionally, in the adjuvant setting, TAC (docetaxel, cyclophosphamide and doxorubicin) is used. On the other side, CAF (cyclophosphamide, 5-fluorouracil and doxorubicin) and CMF (cyclophosphamide, 5-fluorouracil, and methotrexate) regimens are used for nonmetastatic breast cancer in an adjuvant way or alone for metastatic breast cancer. Also used in an adjuvant way is FEC (epirubicin, cyclophosphamide and 5-fluorouracil), for the treatment of metastatic and recurrent breast cancer [45, 46].

However, other combinations exist, such as paclitaxel/trastuzumab and capecitabine/docetaxel [45, 47]. Recently, three kinase inhibitors: dasatinib, afatinib, and trametinib (DAT) potently stopped the proliferation of TNBC (Triple Negative Breast Cancer) cell lines. These experiments may provide evidence for a novel combination module for the treatment of breast cancer, in particular the triple negative form, the most aggressive [48]. Also, a promising combination of drugs for TNBC is the combination of auranofin and vitamin C, presenting a redox-based anticancer activity [49]. Recently, there is a crescent concern in the development of immunotherapy and molecularly targeted therapy combinations for breast cancer of metastatic type. Some examples are the combinations of anti-PDL-1 (programmed death ligand-1) antibodies in combination with HER-2 inhibitors and cyclin-dependent kinase inhibitors [50, 51, 52]. In fact, a growing number of clinical trials are studying combinations of immunotherapy and targeted therapy in breast cancer, with promissory results [53].

Other interesting approach is the combination of drugs that target BACH1 (a transcriptor factor important for metastasis) and the mitochondrial metabolism. In fact, the depletion of this transcription factor sensitized cells to inhibitors of the electron transport chain, such as metformin, being an attractive combination of mechanisms of action for breast cancer therapy [54].

2.4. Drug repurposing

Drug repurposing is an approach to identify a new purpose for existent drugs, approved fot other conditions. It allows fewer costs and a short period of time until the final approval of the drug, rather than a *de novo* developing a drug, because all clinical trial phases have already been executed for the approved agents and the information about side effects, pharmacokinetics and drug interactions have been exposed [55]. There is, therefore, published data on parameters, such as pharmacokinetics and bioavailability, that are accessible to both the clinician and the researcher [19]. However, to establish maximum tolerated doses, for example, for oncologic purposes, phase I trials may still be required. These trials are also needed in the case of the repurposed agent will be tested in untried combinations with different agents, since it must be established that there are no unacceptable toxicities. Anyway, the long drug development process can be shortened by drug repurposing. It can contrast a period of 10–17 year development for *de novo* development versus 3–12 year for repurposed drugs, once repurposing takes into account previous development efforts [19, 56]. To highlight the importance of this methodology, the costs of *de novo* drug development are, on average, 1.5–2.5 billion euros, in contrast to the costs of drug repurposing, which are 250 million euros [57]. Several studies demonstrated cytotoxic activity for agents within a vast range of drug classes that are not originally indicated for cancer. Additionally, more than 10.000 clinical trials investigating drugs in cancer are registered at http://www.clinicaltrials.gov/,[1] but only a few drug candidates progress to the next phase in clinical trials, having an approval rate of cancer drugs entering phase I trials lower than 5%. In 2016, FDA approved only 22 new agents compared to 45 in 2015. In oncology, only 4 new drugs were approved in 2016, in comparison to 14 in 2015. Also, the European Medicines Agency (EMA) approved fewer drugs in 2016 than in previous years [58]. Therefore, the research of drugs approved for non-cancer indications may offer important treatment options for oncological patients. However, despite the growing attraction of this methodology, reports of successful repurposing of drugs as anti-cancer agents have been limited [12]. In this regard, it is notorious that drug repurposing is still in the early stages and a huge number of barriers exist. Despite many strategies being implemented and tested, none has been described as ideal. Furthermore, there is a big divergence of interests by the stakeholders involved in drug repurposing, making this process hard to harmonize. Another important barrier is the fact that companies may be reticent to release information about the drug with the fear that the repurposing program uncovers safety and efficacy issues. However, for rare or severe diseases, issues about safety are softened. Thus, repositioning constitutes a smaller risk for these purposes, even though such agents also produce fewer returns on investment due to their limited target [59].

Ideal drugs for repurposing share several features. They should be drugs that are well studied (well-known), frequently available in the generic form, rather than new drugs, the toxicological profile of this drug must be satisfactory, there should have a verisimilar mechanism of action, suitable for the new disease in question, and support for efficacy at physiological, non-toxic dosages [19].

Ideas for the repositioning process can come from several processes: serendipitous observations, new knowledge about the drugs or from established technology platforms (Figure 1) [13]. Mainly because of the fast advances in technology, nowadays, the serendipity responsible for early discoveries of drugs is being replaced by systematic searches for candidates. Now, it is possible to detect molecular similarities between diseases by examining large and varied datasets. Also, computational models are very important to study the interaction between the

[1] ClinicalTrials.gov is a resource that is provided by the U.S. National Library of Medicine. It is a database where clinical studies conducted in the whole world are present.

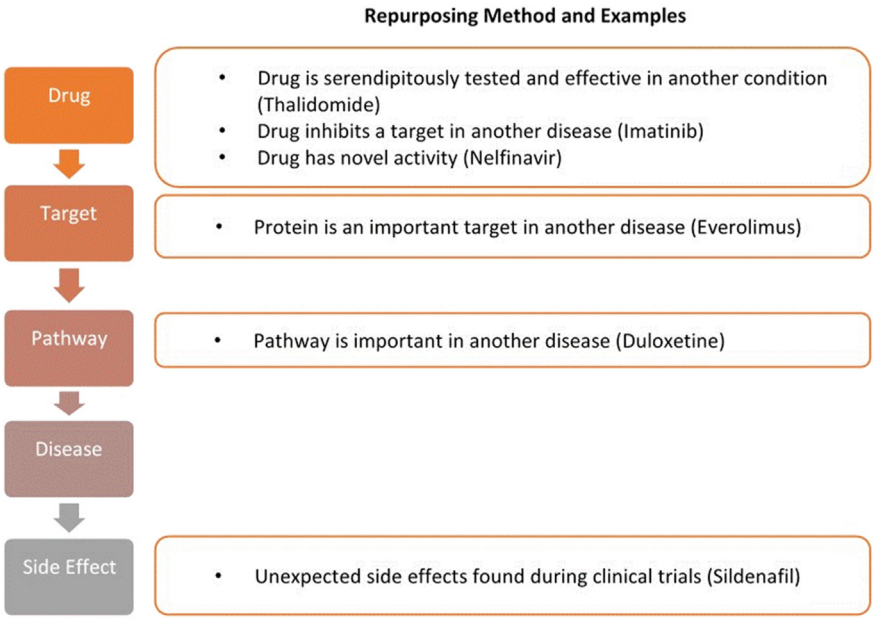

Figure 1. Potential paths of drug repositioning. New indications for existing drugs can come from various processes, since serendipirous observations, until more rational.

molecules and the targets. In turn, high-throughput screening systems can test in a quick way many agents against a great many cell lines. Therefore, the tendency in drug development is focused on drug repurposing based on knowledge, mainly computer-aided repositioning methodologies, replacing rational exploitation of drug side-effects and/or serendipitous discoveries [60, 61].

A great variety of drugs used in the medical practice have, at least, some mechanisms of action that have the potential to be useful in the treatment of cancer. In particular, many off-patent agents have shown proof of efficacy against cancer, in which approximately 50% and 16%, respectively, are highlighted by important human data and by data from one positive clinical trial, at least [62]. Table 3 shows some drug candidates for repurposing and the respective hallmarks of cancer that they may target.

There are several studies in the field of repurposing new drugs for oncologic therapy. It is noteworthy a project, named ReDO (The Repurposing Drugs in Oncology), that consists of international collaboration of diverse research groups and clinicians with the main goal of discovering effective and new cancer treatments, by using existing and well-characterized non-cancer drugs, the potential repurposed cancer drugs. Due to this project, more than 250 non-cancer agents were listed, for which there is pre-clinical and clinical evidence of action in cancer. The basis for this list resides in extensive and active surveillance of the cancer literature [63]. In brief, for oncological purposes, agents like itraconazole, aspirin, chloroquine, verapamil, and all-trans retinoic acid have demonstrated activity in one randomized clinical trial, at least [12, 64]. Particularly, in the case of itraconazole, that specific mechanisms by which it specifically works is unknown, results of a phase 2 study of this drug with Pemetrexed have shown that this combination has potential for metastatic nonsquamous non-small-cell lung cancer, as a second-line therapy [65]. Additionally, other drugs led to responses in rare cancers. For example, tadalafil (PDE-5 inhibitor, indicated for erectile dysfunction), inhibits myeloid-derived suppressor cells in cancer patients [66]. Propanolol (beta-blocker, used for hypertension) decreases proliferation and migration in angiosarcoma models, by blocking beta-adrenergic receptors that are expressed by angiosarcoma cells [67]. Also, metformin has been linked with a positive response to therapy and prolonged survival in a variety of cancers: hepatocellular carcinoma, colorectal, prostate, breast, ovarian, pancreas, esophageal and rectal cancer [58].

Other drugs with randomized trial data that support increased survival include cimetidine (colorectal cancer) and progesterone (breast cancer) [68]. However, data suggests that only thalidomide, ATRA, zoledronic acid and Non-Steroidal Anti-Inflammatory Drugs that inhibit COX-2 enzyme, such as indomethacin and sulindac are currently included in the guidelines of the European Society for Medical Oncology (ESMO) or of the National Comprehensive Cancer Network (NCCN). In the case of the first 3, they were rebranded and reformulated by pharmaceutical companies. In the case of NSAIDs, they are used off-label, being listed in desmoid tumors guidelines [62, 69]. Aspirin, a NSAID, for colorectal cancer, is the only financial orphan drug with positive phase III data, although still not being recommended in clinical guidelines [68].

2.4.1. *Drug repurposing and breast cancer*

In addition to all the approved drugs, some drugs have the potential to be repurposed for the treatment of breast cancer. These drugs can be very interesting to identify biomarkers, to improve long-term surgical

Table 3. Relation between potential drug candidates for repurposing and hallmarks of cancer that they are suggesting to target. Adapted from Reference [49].

Hallmark of Cancer	Potential Drug Candidates for Repurposing
Tumor promoting inflammation	NSAIDs, Thalidomide
Activating metastasis and invasion	Acetylsalicylic acid, Doxycycline, Ritonavir
Inducing angiogenesis	Artesunate, Diclofenac, Disulfiram, Ibuprofen, Nelfinavir, Thalidomide
Resisting programmed cell death	Auranofin, Cardiac glycosides, Disulfiram, Itraconazole, Naproxen
Deregulating cellular metabolism	Auranofin, Metformin, Ritonavir
Sustaining proliferative signaling	Diclofenac, Metformin, Doxycycline, Thalidomide

outcomes and to be given in association with current treatments to increase overall efficacy [70]. There are a variety of drugs, which are being studied, with the potential for being repurposed for breast cancer. One example is the non-selective beta-blocker propranolol. A lot of studies, including a phase II randomized placebo-controlled trial of propranolol combined with another repurposing candidate, etodolac, in women with early-stage breast cancer, showed reduced activity of transcription factors that promote both metastasis and inflammation, decreased epithelial-to-mesenchymal transition and, also, decreased and increased tumor-infiltrating monocytes and B cells, respectively. Another study in early stage breast cancer, by accessing the marker of proliferation Ki67, demonstrated that non-selective beta blockade reduced the proliferation of the tumor by 66%, [71]. In fact, a huge number of studies have demonstrated the anti-proliferative, anti-angiogenic, anti-migratory and cytotoxic activities of a diversity of β-blockers [72, 73]. *In vivo* results showed that isoproterenol, metaproterenol and formoterol (all β agonists) stimulated in a significant way breast cancer cell metastasis' growth, highlighting the role of β receptors in breast cancer [74, 75]. Another example is chloroquine, with very interesting results in several breast cancer cell lines and trials of phase I, either as a single agent or combined with other agents [76, 77]. Results in mice showed that this drug increased survival time and reduced primary tumor volume, the number and the diameter of lung metastasis [78]. Other potential drugs for breast cancer treatment are the angiotensin receptor blocker losartan and disulfiram which, respectively, completely inhibited the formation of the tumor in 20% of treated mice and showed a significant reduction in tumor burden in a mammary tumor model and, in breast cancer stem cells resistant to radiation, induced immunogenic cell death [79, 80, 81]. Additionally, many retrospective studies report that NSAIDs could reduce recurrences of breast cancer. With special importance, a phase III study with ketorolac in breast cancer surgery is being performed, suggesting that this NSAID may be another potential drug to repurpose [82, 83]. Salinomycin (antibiotic) is another drug that has the potential to be repurposed for breast cancer [84]. Studies show that this drug can inhibit tumor growth and expression of cancer stem cell genes in *vivo*, as well as induce cell cycle arrest in combination with panobinostat, a histone deacetylase inhibitor [85]. Concerning itraconazole, an anti-fungal drug, a pilot trial accessed its pharmacokinetics parameters in 13 patients with breast cancer of metastatic type. This study led to the observations that more plasma levels of this drug led to higher levels of angiogenesis inhibitors and decreased levels of angiogenic factors [86]. Additionally, in combination with 5-Fluorouracil, Itraconazole has been shown to reduce MCF-7 cells (breast cancer cells) proliferation and viability. In this same study, Tacrine or Verapamil, in combination with 5-Fluorouracil, also showed a reduction in MCF-7 cells' proliferation and viability [87]. An anthelmintic named niclosamide has also shown potential to be used in breast cancer. In a study, this drug reversed epithelial-mesenchymal transition and inhibited stem-like phenotype of cells [88, 89]. Statins have also shown promising results [90]. An increase in apoptosis and in radiosensitivity, as well as inhibition of invasion and proliferation, was observed in various breast cancer cell lines (MDA-IBC3, Sum149, and Sum190). Clinical trials in patients with breast cancer support these findings by the demonstration of an improvement in local control and a mortality reduction for the patients that use statins [91]. Computational studies with antivirals, such as ombitasvir (a drug used in hepatitis C) have shown, also, that this drug could be repurposed for the prevention and control of breast cancer [92]. In this line of antivirals, studies with cell lines and mice with nelfinavir have shown promising results in HER2 positive breast cancer treatment trials with the same dose used in HIV patients [93]. Other potential drugs to be repurposed for breast cancer are the class of antipsychotics named phenothiazines (Thioridazine, Fluphenazine and Trifluoperazine). In vitro, these drugs reduced cell invasion, proliferation and increased cell death in triple negative breast cancer cells. Also, in *vivo*, there was a reduction of tumor growth by the administration of these antipsychotics to mice having xenografts of MDA-MB-231 triple negative breast cancer [94]. Another drug with the potential to be repurposed for breast cancer therapy is aspirin. With regular aspirin use, multiple observational studies reported an improvement in breast cancer survival [95]. Besides inhibiting cyclooxygenase-2, this drug also modulates pathways implicated in cancer, including NFκB and mTORC1 [96]. Additionally, combination therapy of metformin for the management of breast cancer is also a promise. Namely, metformin has been combined with Doxorubicin [97], 5-Fluorouracil [98], Propranolol [99] and Vitamin D3 [100], with excellent results in reducing cell viability by inhibiting NF-kB expression, induction of DNA damage by a metabolic crisis, inhibition of glucose metabolism and increasing apoptosis, respectively.

Breast cancer, despite a great variety of approved therapeutic agents and drugs with potential to be repurposed, remains an alarming healthcare problem. The costs and difficulties in the organization of screening programs make these programs hard to execute. Highly qualified healthcare providers and appropriate conditions in operation rooms are important for a suitable surgical treatment. Additionally, advanced treatment modalities involving radiation are hard to achieve in, particularly, countries in development. Appropriate treatments, management of eventual secondary effects, advanced targeted therapies are expensive, and the most recent treatment modalities need advanced and expensive pathology, including immunohistochemistry and molecular pathologic analysis. Additionally, the issue of the diverse drug resistance mechanisms, common to the majority of cancer types, remains a problem that is difficult to combat, requiring a lot of research [101].

3. Concluding remarks

Cancer is a complex disease that includes a huge number of pathways and molecules, being challenging to treat effectively. Therapy for this disease, which encompasses the therapy for breast cancer, is continuously more studied, in which therapeutic modalities, such as drug repurposing and combination, are being broadly addressed.

Drug repurposing and drug combinations are major approaches applied to improve cancer therapy, reducing its toxicological profile, and improving its efficacy. However, despite the growing investigation and interest in these methodologies, there are still limitations, namely financial and toxicological issues.

Investigating drug combination and drug repurposing approaches in breast cancer therapy can be an important focus of studies, as it can greatly improve its treatment, namely the metastatic type, that has still many barriers to effective treatment.

Declarations

Author contribution statement

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Data availability statement

Data included in article/supplementary material/referenced in article.

Declaration of interests statement

The authors declare no conflict of interest.

Additional information

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