REVIEW ARTICLE

Does Therapeutic Repurposing in Cancer Meet the Expectations of Having Drugs at a Lower Price?

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Abstract

Therapeutic repurposing emerged as an alternative to the traditional drug discovery and development model (DDD) of new molecular entities (NMEs). It was anticipated that by being faster, safer, and cheaper, the development would result in lower-cost drugs. As defined in this work, a repurposed cancer drug is one approved by a health regulatory authority against a non-cancer indication that then gains new approval for cancer. With this definition, only three drugs are repurposed for cancer: Bacillus Calmette–Guerin (BCG) vaccine (superficial bladder cancer, thalidomide [multiple myeloma], and propranolol [infantile hemangioma]). Each of these has a different history regarding price and affordability, and it is not yet possible to generalize the impact of drug repurposing on the final price to the patient. However, the development, including the price, does not differ significantly from an NME. For the end consumer, the product's price is unrelated to whether it followed the classical development or repurposing. Economic constraints for clinical development, and drug prescription biases for repurposing drugs, are barriers yet to be overcome. The affordability of cancer drugs is a complex issue that varies from country to country. Many alternatives for having affordable drugs have been put forward, however these measures have thus far failed and are, at best, palliative. There are no immediate solutions to the problem of access to cancer drugs. It is necessary to critically analyze the impact of the current drug development model and be creative in implementing new models that genuinely benefit society.

Key Points

Drug repurposing results in lower-cost drugs for cancer.

The few drugs approved for cancer are indistinguishable from novel medications.

We must critically analyze the current drug development model and be creative in implementing new models that benefit society.

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1 Cancer Epidemiology

A projection of global cancer statistics estimated there were 18.1 million new cancer cases and 9.9 million deaths in 2020 [1]. While mortality is plateauing or decreasing for some common cancers in high-income countries (HICs), these are having an increased incidence and mortality in low-income (LICs) and middle-income countries (MICs) [2]. In the US, overall cancer death rates decreased by 2.3% and 1.9% per year among males and females, respectively, from 2015 to 2019 [3]. On the other hand, the Global Burden of Disease 2019 Cancer Collaboration discloses that the age-standardized mortality and incidence rates increased from 2010 to 2019 in countries with the lowest sociodemographic index (SDI) but decreased in the high–middle and high SDI quintiles, with the most significant decrease in the high SDI quintile [4].

2 Approaches to Reduce Cancer Mortality

Reducing mortality from cancer is the primary goal that society, governments, medical, and scientific communities face. Significant attempts at reducing cancer mortality can be made by primary and secondary prevention or screening. One-third (35%) of seven million cancer deaths could be preventable through primary prevention [5], and cancer mortality can also be reduced through secondary prevention.

Early cancer detection improves cancer outcomes. Thus far, screening for a few neoplasias (breast, cervix uteri, colorectal, and lung) is of proven value in reducing mortality to a different extent in countries with organized screening efforts [6, 7]. Paradoxically, most medical, scientific, and pharmaceutical organizations focus on improving treatments (tertiary prevention) by developing new molecular entities (NMEs). Unfortunately, the 124 NMEs approved by the US FDA between 2003 and 2021 increased the patient median survival by 2.8 months [8]. Although the benefits of globally reducing cancer mortality through tertiary prevention or treatment are limited, oncological research continues with this model.

3 Cancer Drug Worldwide Affordability

A substantial proportion of cancer patients worldwide do not access or receive adequate care, mainly because of weak health systems, inadequate national services, and disparities in access to cancer care [9]. For instance, only 15% of cancer patients from LICs and MICs may have access to drugs such as trastuzumab, bevacizumab, cetuximab, erlotinib, gefitinib, and sorafenib [10]. Trastuzumab is used under a very restrictive policy in public institutions in Latin American countries [11]. Likewise, in India, the cost of a typical trastuzumab course for metastatic breast cancer is approximately 15 times the per capita monthly income of an average Indian citizen [12]. This simple example indicates that only a minority of privileged patients living in LICs and MICs who have a private insurance program can have their HER2-positive breast cancer properly treated. On the other hand, patients and their families that can afford cancer treatment may suffer from financial and emotional stress.

4 Financial Toxicity

Even in HICs, cancer treatment costs are an issue. It is no surprise that 'financial toxicity', defined as "the problems patients have related to the cost of medical care", is now common. As with any adverse effect of cancer treatment, the experience of financial toxicity can generate changes in household spending, to personal bankruptcy [13]. The COmprehensive Score for financial Toxicity (COST), which correlates with health-related quality of life (HRQoL), demonstrates that financial toxicity is a clinically relevant patient-centered outcome [14]. The most challenging issue about financial toxicity that requires further study is the higher risk of death in patients who experience it. In a study on 231,586 cancer patients, the adjusted hazard ratio for mortality among patients with cancer who filed for bankruptcy versus those who did not was 1.79 [15].

5 Drug Repurposing for Cancer, and Cancer Drug Affordability

Before discussing cancer drug repurposing, it is helpful to provide a general overview of the development of anticancer drugs. From the scientific point of view, we can consider two stages in the pharmacological therapy of cancer. The first period was from 1945 to 1997, when cytotoxic chemotherapy and hormone therapy drugs were developed, ending with the launch in 1998 of the first molecular therapy agent or targeted therapy, rituximab, a monoclonal antibody against CD20. Since then, more than 250 agents have been approved, including small molecules, antibodies, and, more recently, cell therapies. A distinguishable phenomenon emerged, further marking the differences between these two periods. The price of cancer drugs in the US skyrocketed around 1998. Inflation-adjusted analyses show that the price of patented anticancer drugs is often increased after launch, by as much as 44% over a decade [16].

Drug repurposing surged, to overcome the pharmaceutical industry's limited productivity and the enormous increases in pharmaceutical research and development (R&D) spending under the conventional drug discovery and development model (DDD). The DDD entails targeting discovery and validation, lead identification by high-throughput screening, and lead optimization in medicinal chemistry. The repurposed approach can reduce the risk of failure in developing NMEs. Specifically, repositioning candidates have already demonstrated safety in the clinic, allowing bypassing of early clinical steps, and in sum, development costs can be lowered. Accordingly, drug repurposing is considered 'safer, faster, and cheaper'. Ashburn and Thor discussed these concepts in 2004, the first to be published in the scientific literature on the current view of drug repurposing [17].

However, drug repurposing is not as recent as it could appear. In 2019, Baker et al. conducted a bibliometric review of drug repurposing by scanning > 25 million papers in the PubMed database (dating from 1952), using text-mining methods to gather, count, and analyze chemical–therapeutic disease relationships. They found that > 60% of the approximately 35,000 drugs or drug

candidates were tried in more than one disease, including 189 drugs that were tried in more than 300 diseases each. Baker et al. concluded, "Our results show that the number of drugs repurposed for new indications is surprisingly high. Data show that nearly two-thirds of all drugs annotated in MEDLINE were tried on at least one disease beyond the original use, and several hundred drugs in scores of diseases" [18].

Since 2004, after the Ashburn and Thor publication [17], a simple PUBMED search using drug repurposing yielded 11,303 hits at the time of writing this article (December 2022). Part of this enthusiastic view on cancer drug repurposing stems from the widespread belief that this approach would ultimately result in more affordable cancer drugs. It is common to see media headlines featuring this drug development approach as follows:

"Cheap, 'safe' drug kills most cancers" [19]; "A low-cost drug from the 1960s could help treat colon cancer" [20]; "Could cheap drugs be the new way to tackle cancer?" [21]; "Cheap drug for common cold can stop spread of cancer" [22]; and "Could these cheap drugs hold a cure for cancer?" [23].

There is no unifying definition of drug repurposing. One of the most inclusive definitions could be "A general concept of branching the development of an active pharmaceutical ingredient at any life cycle stage" [24]. A more common definition of *cancer drug repurposing*, and the one used in this work, is a drug previously approved by a regulatory agency for a non-malignant condition that gains new approval for a cancer indication. Several drugs are touted as repurposed cancer drugs; however, their first approval was for cancer and therefore they failed to meet the definition.

6 Drugs Widely Referred to as Repurposed for Cancer but Have Been Anticancer Drugs Since the Beginning

6.1 Dexamethasone, Prednisolone, Prednisone

Glucocorticoids are perhaps the most well-known medication in human medicine. The first clinical evidence that an extract of animal adrenocortical tissue could counteract human adrenal failure occurred in 1930. In 1948, the first patient with rheumatoid arthritis was treated with cortisone, and soon after that, other rheumatologic patients were treated [25]. The first ever FDA-approved glucocorticoid was Flo-Pred (prednisolone acetate) suspension for oral use in 1955, and among its indications, cancer was included. The indications were (1) as an anti-inflammatory or immunosuppressive agent for certain allergic, dermatologic, gastrointestinal, hematologic, ophthalmologic, nervous system, and renal diseases; (2) for respiratory, rheumatologic, specific infectious diseases or conditions and organ transplantation; (3) for the treatment of certain endocrine conditions; and (4) for the palliation of certain neoplastic conditions (Table 1). Among these malignancies were acute leukemia and aggressive lymphomas. Thus, since their approval, these drugs have been considered cancer therapy, which was not surprising. In 1944, it was shown that cortisone caused tumor regression in transplantable mouse lymphosarcoma, a finding that soon extended to various murine lymphatic tumors. The effects of corticosteroids were also evaluated on many non-endocrine and non-lymphoid transplantable rodent tumors. Pharmacologic doses of steroids inhibited the growth of various tumor systems, and tissue culture studies confirmed that lymphoid cells were the most sensitive to glucocorticoids, and responded to treatment with decreases in DNA, RNA, and protein synthesis [26]. Its uses as an antitumor agent have been formally incorporated into the MOPP (Mechlorethamine, vincristine (Oncovin), Procarbazine, and Prednisone) regimen for Hodgkin disease since 1964 and in the multidrug regimens for acute lymphoblastic leukemia since 1965. As such, glucocorticoids cannot be considered repurposed for cancer.

Table 1 Common drugs considered repurposed for cancer but whose first approval was for cancer

Drug	First indication	Year of first US FDA approval
Glucocorticoids	Acute leukemias	1955
	Aggressive lymphomas	
Progestogens	Recurrent and metastatic endometrial and renal cancer	1960
Somatostatin analogs	Pituitary tumors	1998
	GEP-NETs	
Bisphosphonates	Hypercalcemia of malignancy	1987
	Breast cancer metastases	
	Osteolytic bone metastases (MM)	
	Osteolytic bone metastases (ST)	
All-trans retinoic acid	Acute promyelocytic leukemia	2000
Arsenic trioxide	Acute promyelocytic leukemia	2000

GEP-NETs gastroenteropancreatic neuroendocrine tumors, *MM* multiple myeloma, *ST* solid tumors

The list may not include all of this category

6.2 Medroxyprogesterone, Megestrol Acetate

The first orally active progestin, ethisterone, was synthesized in 1938. Progesterone and its related molecules are crucial in modern clinical practice, particularly in reproductive medicine [27]. Medroxyprogesterone (Depo-Provera) was FDA-approved in 1960 as an anticancer agent, specifically as adjunctive therapy and palliative treatment of inoperable, recurrent, and metastatic endometrial or renal carcinoma [28]. Megestrol acetate was also FDA-approved for endometrial cancer in 1971 [29]. The current FDA label of medroxyprogesterone indicates its use for pregnancy prevention and managing endometriosis-associated pain. In contrast, megestrol acetate is indicated for treating anorexia, cachexia, or an unexplained significant weight loss in patients diagnosed with acquired immunodeficiency syndrome. Currently, both drugs are included in National Comprehensive Cancer Network (NCCN) guidelines for treating endometrial and breast carcinoma, as well as in low-grade endometrial stromal sarcoma.

6.3 Somatostatin Analogs: Octreotide, Lanreotide, and Pasireotide

Somatostatin is a hormone with antisecretory, antiproliferative, and immunomodulatory activities helpful in treating various diseases, including cancer. Currently, there are three synthetic somatostatin analogs in clinical use—octreotide, lanreotide, and pasireotide. The FDA first approved octreotide in 1988; lanreotide was approved for acromegaly treatment in Europe in the 1990s and FDA-approved in 2007; and pasireotide was approved by the FDA in 2014. These three analogs with different formulations are labeled for acromegaly (cases where surgery is not appropriate, after the failure of surgery and radiotherapy, or in the interim period until radiotherapy is entirely effective). For symptoms associated with gastroenteropancreatic neuroendocrine tumors (GEP-NETs): for unresectable well- or moderately differentiated locally advanced or metastatic GEP-NETs and other non-malignant conditions such as prevention of complications after pancreatic surgery and upper gastrointestinal hemorrhage due to gastroesophageal varices in patients with cirrhosis [30, 31].

6.4 Bisphosphonates

Bisphosphonates are pyrophosphate analogs. This drug class is used in the therapy of several bone diseases characterized by an imbalance between osteoblast-mediated bone production and osteoclast-mediated bone resorption. Bisphosphonates were developed in the 19th century but were first investigated in the 1960s for use in disorders of bone metabolism. Their synthesis occurred in 1965 [32] and their effects on calcium phosphate metabolism were evaluated in 1968 [33] and first administered in a patient with myositis ossificans in 1969 [34]. In the 1970s, bisphosphonates were investigated in osteoporosis, Paget's disease of bone, and cancer [35–37]. Etinodrate was first approved for hypercalcemia of malignancy in 1987. Currently, there are several bisphosphonates in clinical use, i.e. alendronate, risedronate, ibandronate, zoledronate, and alendronate. Individual labeling varies for each of these. Among the non-malignant indications of bisphosphonates are Paget's disease, osteoporosis, prevention of osteoporosis, hypercalcemia, heterotopic calcification, spinal cord injury, and heterotopic calcification total hip arthroplasty. Labeled malignant conditions are (1) breast cancer metastases (pamidronate); (2) hypercalcemia of malignancy (pamidronate and zoledronate); (3) osteolytic bone lesions of multiple myeloma (pamidronate and zoledronate); and (4) osteolytic bone metastases of solid tumors (zoledronate).

6.5 All-Trans Retinoic Acid and Arsenic Trioxide

All-trans retinoic acid (ATRA) has been used since 1962 for skin conditions [38]. The first Chinese experience with ATRA in 1988 reported a complete response in 23 of 24 patients with acute promyelocytic leukemia (APL) [39]. Afterward, several studies in collaboration with the West [40] led to the approval of this agent by the FDA in 2000 [41]. It is important to emphasize that the discovery of ATRA as an antileukemic agent occurred before the molecular pathology of APL was known. The first indication that arsenic could be helpful in leukemia occurred in the 1880s, demonstrating that an arsenic solution reduced leukocytosis [42]. Fifty years later, before the onset of cytotoxic chemotherapy, it was used to treat chronic myeloid leukemia [43]. Chinese investigators published the first results on APL treatment with arsenic trioxide (ATO) in the late 1990s. A study reported complete rates with ATO as a single agent of up to 73% and 50% in newly diagnosed and relapsed APL patients [44]. The results were replicated in relapsed APL patients after first-line treatment with ATRA [45], and a multicenter trial in the US [46] led to its FDA approval in 2000. The combined use of ATO and ATRA as the first-line treatment of APL was adopted in 2013 [47].

7 Truly Repurposed Cancer Drugs Whose First Regulatory Labeling was for Non-Cancer Conditions

7.1 Bacillus Calmette–Guerin (BCG) Vaccine

The Bacillus Calmette–Guerin (BCG) vaccine is used for the prevention of tuberculosis (Table 2) and is currently used in many countries with a high prevalence of the disease to prevent childhood tuberculous, meningitis, and miliary disease. The FDA approved this vaccine in 1989. BCG is not routinely used in the US because of the low risk of infection with Mycobacterium tuberculosis [48]. The clinical use of BCG as cancer therapy began in 1969 when Mathé, in France, reported encouraging results with BCG as adjuvant therapy for acute lymphoblastic leukemia [49]. Furthermore, in 1970, Morton, in the US, observed regression of malignant melanoma treated with intralesional BCG [50]. Regarding bladder cancer, Coe and Feldman demonstrated a strong delayed hypersensitivity reaction to BCG in the guinea pig bladder [51], while Bloomberg et al. reported on cellular infiltration in the bladder of dogs receiving intracavitary BCG [52]. Based on these observations, Morales, a urologist in Canada published the first use of intravesical BCG against superficial bladder cancer in 1976 [53]. In 1997, the FDA approved the general use of intravesical BCG (TICE BCG) in patients with superficial bladder tumors. Thirty years after the first report, BCG therapy remains the recommended standard treatment of high-grade non-invasive bladder cancer [54].

7.2 Thalidomide

Thalidomide was introduced in Europe as a sedative in the late 1950s and subsequently withdrawn in 1961 when it was shown to be teratogenic, causing severe infant limb defects when administered to pregnant women. Several decades later, thalidomide demonstrated potent activity in erythema nodosum leprosum, and subsequent studies found it beneficial in several autoimmune conditions and cancers. The FDA first approved thalidomide in 1998 against erythema nodosum leprosum, a painful inflammatory condition associated with Hansen's disease [55]. The anticancer activities of thalidomide were described in 1965 [56]. These data led to the first study in 84 refractory (90% had received high-dose chemotherapy) myeloma patients using single-agent thalidomide. The results showed an overall response rate of 32%. At 12 months of median follow-up, the progression-free survival (PFS) and overall survival (OS) rates were 22% and 58%, respectively [57]. In 2006, the FDA approved Thalomid (thalidomide) combined with dexamethasone to treat newly diagnosed multiple myeloma based on a randomized, double-blind, placebo-controlled trial [58].

7.3 Propranolol

In 1948, Ahlquist described for the first time the existence of the α- and β-adrenotropic receptors as the site of action of catecholamines [59], while in the 1960s, Black developed propranolol, the first β-blocker approved by the FDA in 1967 for the treatment of coronary artery disease and blood hypertension [60]. Since then, several β-blockers have gradually replaced propranolol, mainly in cardiovascular disease. However, propranolol and its generics continue to be widely prescribed [61]. The first observations of the antitumor effects of propranolol date back to 1966 against pheochromocytoma, but it was not until 2008 when Léauté-Labrèze et al. demonstrated its therapeutic utility for infantile hemangioma in 11 patients [62]. Additional small trials culminated in results from a multicenter, randomized, double-blind trial assessing a pediatric-specific oral propranolol solution in infants 1–5 months of age with proliferating infantile hemangioma requiring systemic therapy [62]. This study started in 2010, was published in 2015, and was funded by Pierre Fabre Dermatologie, leading to its EMA approval in 2014 [63]. In that study, among 460 randomized infants, 456 received treatment. The regimen of 3 mg/kg of propranolol daily for 6 months demonstrated successful (complete or nearly complete resolution of the target hemangioma) results over placebo (60% vs. 4%; $p < 0.001$). Only 10% of patients in whom treatment with propranolol was successful required systemic retreatment during follow-up. The common adverse events associated with propranolol (hypoglycemia, hypotension, bradycardia, and bronchospasm) infrequently occurred, with no significant difference

Table 2 Repurposed cancer drugs but whose first approval was for non-cancer conditions

Drug	First-approval	Year	Cancer approval	Year
BCG	Tuberculosis vaccine	1989	Superficial bladder cancer	1997
Thalidomide	Erythema nodosum leprosum	1998	Multiple myeloma	2006
Propranolol	CHD and HBP	1967	Infantile hemangioma	2014

BCG Bacillus Calmette–Guerin, *CHD* coronary heart disease, *HBP* high blood pressure

in frequency over placebo [62]. Postmarketing surveillance drug study supports the efficacy and good tolerance of propranolol (Hemangiol) in children with infantile hemangioma [64].

8 Cheaper, Faster, and Safer: The Premises of Drug Repurposing

8.1 Cheaper

The total cost of bringing a new drug to the market of an NME from pharmaceutical companies under the classical DDD was recently calculated to be as high as US$2870 million, including post-approval R&D costs [65]. On the contrary, the cost of drug repurposing averages US$8.4 million. Others estimated a cost of around US$300 million, assuming that the repurposing candidate must undergo phase II and III clinical trials [66, 67]. Nevertheless, it still represents an approximately 85% saving. Thus, bringing a repositioned drug to market seems to cost much less. From a purely financial perspective, it is clear that repurposing is an entirely different investment needed to create a new drug product in the market.

8.2 Faster

The average time required from drug discovery to marketing can be as long as 15 years for NMEs under the current DDD [68, 69]. Based on the model by Paul et al., it is estimated that this requires approximately 6.5 years for a repurposed drug, almost 10 years less [67]. Reduced time would result in considerable savings for taking the repurposed drugs through regulatory approval.

8.3 Safer

The initial screening of compound libraries [70–72] leads to selecting a single compound, which only has an approximately 8% chance of succeeding in clinical trials [73]. Existing drugs that are well tolerated in late-stage trials but fail to meet the endpoints of their first indication have reduced development risk into potentially new indications. They can do so if proven effective in the new indications and sufficiently differentiated against the standard of care. When such drugs enter clinical trials, the concern is not safety but efficacy. Since safety accounts for approximately 30% of drug failures in clinical trials, this is a significant development advantage that repositioned drugs enjoy. Because of this, drug repurposing has a higher success rate. It is estimated that 10% of NMEs get to the market from phase II clinical trials and 50% from phase III trials. In contrast, the corresponding rates for repurposing compounds are 25% and 65%, respectively [66].

The premises on the virtuousness of drug repurposing, specifically for cancer, are simple. Common sense would suggest that if drugs are developed faster, cheaper, and safer (less risky to fail), the repurposed drug should have cost less. How do the BCG vaccine, thalidomide, and propranolol stand in this regard?

9 Faster, Safer, and Cheaper: Are These Premises Met for the BCG Vaccine, Thalidomide, and Propranolol?

9.1 BCG Vaccine

9.1.1 Faster

The FDA approval occurred in 1997 in a retrospective analysis of patients treated with TICE BCG under six different investigational new drugs (IND), updated in 1989, and two randomized trials published in 1993 and 1995. According to this information, the development could have taken around 8 years.

9.1.2 Safer

At the time of its development, there were no significant safety concerns, as the first trial was published in 1986 [74].

9.1.3 Cheaper

The two randomized trials [75, 76] were funded by the Dutch South-East Cooperative Urological Group and the second was funded by the SWOG, which was supported in part by the National Cancer Institute. No reference is made to industry funding. According to this information, we can suggest that its development was cheaper for the industry.

9.2 Thalidomide

9.2.1 Faster

This agent was approved based on a phase II study between December 1997 and June 1998, and reported a median follow-up time of 17 months. Its approval took place in 2006, hence the development time can be estimated as 9 years.

9.2.2 Safer

At the time of its development for multiple myeloma, there were no significant additional concerns regarding safety.

9.2.3 Cheaper

The USA National Cancer Institute partly supported the study. Simultaneously, Celgene Corporation contributed

to data collection, analysis, and free provision of the study drug. According to this information, we can say that its development was cheaper for the industry.

9.3 Propranolol

9.3.1 Faster

This agent was approved, based on a phase III study, between February 2010 and November 2011. The results were published in February 2015 [62], whereas the approval occurred in 2014 (a total of 4 years).

9.3.2 Safer

When the phase III trial was performed, there were no significant concerns regarding safety.

9.3.3 Cheaper

The first clinical study on 11 patients treated with propranolol did not report that the work was funded by industry [77]. Among the two subsequent small, randomized trials, Hogeling et al. reported no funding source [78], while the funding source for the Leaute-Labreze study was the University Hospital of Bordeaux, France [79]. Pierre Fabre Dermatologie supported the randomized trial [62], leading to its approval. An estimate based on an average cost for a randomized trial is US$20 million, and the average for a phase III trial of new drugs approved by the FDA is US$41,117 per patient [80]. In this case, with 460 patients, the cost could have been US$18.9 million, very well into the range of US$8–300 million for a repurposed drug [66, 67].

10 Affordability of the Repurposed Drugs for Cancer: BCG Vaccine, Thalidomide, and Propranolol

10.1 BCG Vaccine

Intravesical BCG is used following transurethral resection of bladder tumor for intermediate- and high-risk non-muscle-invasive bladder cancer. A regimen comprises an induction with at least five intravesical instillations of BCG within 70 days from the BCG therapy start date. Adequate maintenance BCG therapy was defined as at least seven instillations within 274 days of the first instillation [81]. A vial of 50 costs around US$160 for approximately 12 doses per year, hence the monthly cost is around US$160. For this product, the limited profit in its production is one of the issues responsible for recurrent shortages of production supplies [82].

10.2 Thalidomide

Even before thalidomide was FDA-approved for multiple myeloma in 2006, thalidomide was widely used off-label for multiple myeloma and other hematological cancers and solid tumors, which allowed Celgene to raise the price of Thalomid by almost 400%, from $6.00 to $29 per 50 mg capsule between 1998 and 2004 [83]. Another analysis of outpatient spending shows that median monthly spending on thalidomide increased from $1869 to $7564 between 2000 and 2014 [84]; 400 mg daily for multiple myeloma is around US$20,000 per month [85].

10.3 Propranolol

At a recommended dose schedule of 1.5 mg/kg twice daily at US$327 per bottle of 120 mL (450 mg), the approximate monthly cost of the brand name Hemangeol could be approximately US$327 [86]. Using a generic preparation with 450 mg of propranolol in 120 mL excipient (cost of 40 mg tablet US$0.122, the monthly cost could be only US$0.14 (calculated based on the information provided by the Canadian Agency for Drugs and Technologies in Health [87]).

A primary reason therapeutic cancer repurposing gained notoriety was that it was advertised as a way to have cheap drugs for the population, since, in its purest form, it refers to the prescription of widely available, patent-free, and low-cost drugs already in clinical use before approved for cancer. We identified only three repurposed drugs because these were first approved by the regulatory health authority for a non-cancer indication and then had subsequent approval for a cancer indication. Because there were only three drugs with these characteristics, is not possible to generalize about the final price to the patient. However, the entire developmental process up to commercialization, including the price, does not differ significantly from an NME. Thus, for the end consumer, the product's price is unrelated to whether it followed the classical development or the abbreviated repurposing.

10.4 BCG Vaccine, Thalidomide, Propranolol

Each of these three has a different history regarding price and affordability. For BCG, the main problem is its recurrent worldwide shortage due in part to detected safety issues in its production, the small number of manufacturers, and the complexity of its elaboration. This shortage affects not only children who benefit from vaccination against tuberculosis but also patients with bladder cancer. Ironically, a product that can save so many lives is precisely its low-cost and low-profit potential, resulting in unnecessary suffering and

death. Thalidomide appears to be the opposite. Even before its approval for cancer in 2006, it was widely used off-label for multiple myeloma and other hematological cancers and solid tumors; therefore, Celgene Corporation raised its price from US$1440 (monthly at a daily dose of 400 mg) in 1998 to US$20,000 in 2022 (13.8-fold higher). Thus, although Celgene contributed only to data collection, analysis, and free provision of the study drug for the randomized phase III trial, lending to its approval in multiple myeloma, the end consumer price appears to be out of proportion with the investment in drug development. For propranolol, regardless of whether a US$327 monthly cost can be considered low or high, this price is 2000-fold higher than the cost of generic preparation with 450 mg of propranolol in 120 mL excipient. The price could also appear out of proportion if taken into account that Pierre Fabre Dermatologie could have invested approximately 18.9 million in the randomized phase III trial leading to its approval. The preceding questions the myth created by the pharmaceutical industry that the costs of medicine need to be high to cover the R&D costs. It is known that the industry spends almost twice more on marketing than on R&D. Importantly, prices are not set based on a particular acceptable profit level or production cost. Prices are established based on a calculation of the maximum amount people are willing to pay, also known as value-based pricing or willingness-to-pay (WTP). The seriousness of a cancer diagnosis plays a significant role in adopting this pricing strategy [88]. The high prices of chemotherapy drugs are subjected to several in-depth reviews [89–93] and are not discussed in this article. It may suffice to say that cancer care should not be seen as any other good or service of a 'free market' system, as the traditional checks and balances that make the free-market system work so efficiently in all other areas are absent when it comes to most cancer treatments.

11 Barriers to be Overcome in Drug Cancer Repurposing

Beyond the fact that drug prices are not related to how they were developed, the development and prescription of repurposed drugs must overcome two additional barriers. The main barrier is economical. The current expenses on clinical trials are too much for non-industry initiatives to handle—perhaps too much for anyone to handle if a drug is off-patent and there is no money to be made. Among the 190 registered clinical trials researching any of the 72 drugs linked to the Repurposing Drugs in Oncology (ReDO) Project, only 1% and 3% are sponsored by a large or small/medium-sized pharmaceutical company. A university or a hospital performs 67%, 28% by specific research centers or non-profit organizations, and 2% by government agencies [94].

A second barrier to overcome in repurposing drug development is prescription bias. Unfortunately, the scientific evidence from clinical trials may not be enough for oncologists to prescribe. For NMEs, massive spending from pharmaceutical companies on advertising their novel drug products and securing health regulatory authorities approval. Additionally, pharmaceutical companies pay vast amounts of money to 'opinion leaders' to promote the prescription, most commonly in 'educational lectures'. In 2018 only, the number one doctor in the top ten paid received $24 million. For further information on the data, readers are welcome to visit the ProPublica web page [95].

On the contrary, lack of advertising also results in a negative prescription bias, as is the case with aspirin. In 2003, a placebo-controlled trial of aspirin showed statistically significant positive results as a chemopreventive agent [96]. Among 635 patients with primary colorectal cancer, daily aspirin (325 mg) significantly reduced the risk of developing new adenomas, with no increased risk of bleeding. This finding is supported by meta-analyses of various observational studies [96, 97]. However, aspirin has neither been approved nor recommended in any clinical guidelines for this purpose. Thalidomide is another example of prescription bias. Despite the proven efficacy and safety of thalidomide for multiple myeloma, well-recognized guidelines, such as the NCCN [98], do not recommend thalidomide for the first-line or maintenance treatment for this hematological condition. Despite this, two randomized, phase III clinical trials failed to show the survival advantage of melphalan-prednisone-lenalidomide over melphalan-prednisone-thalidomide [99, 100]. It is noteworthy that thalidomide is not widely used in the US, although lenalidomide costs about 43-fold more than thalidomide [101, 102].

12 Perspectives

The option that could meet the expectations of having medicines at affordable prices for the population would be that non-profit organizations carry out repurposing. Perhaps in this scenario, the industry could only participate in the registration and commercialization of the previous agreement on price between the organization that carried out the development and the industry registering the product. Currently, there are several non-profit organizations for the therapeutic repurposing of cancer, including the USA CuresWithinReach, UK-based FindaCure and GlobalCures, and the Belgian AnticancerFund, among others [103]. One of the most prominent efforts at repurposing cancer is the ReDo project, a collaboration between the Anticancer Fund and GlobalCures. This joint effort uses a literature-based approach to identify licensed non-cancer drugs with published evidence of anticancer activity. Data from 268 drugs

were included in a database (ReDO_DB). Some of these candidates for repurposing are currently in clinical trials [94]. However, thus far, there are no products among these candidates that have completed their development, therefore we cannot predict if they will meet the repurposing expectations regarding affordability.

Even assuming that non-profit organizations could carry out therapeutic repurposing in cancer until registration, commercialization, and prescription, we must not forget that these organizations' commercial aspect, in general, is always present. The term philanthrocapitalism has been coined for this remarkable trend of business-foundation collaboration, promoting philanthropic generosity and the billionaires' social goodwill to 'save the world'. Beyond doubt, the US philanthropy's US$2 billion annual spending significantly impacts the international health and development arena. The philanthrocapitalist approach has been questioned. Essentially, it is known that the accommodation of private capital fundamentally changes the character and culture of public and non-profit institutions. Over time, non-profit institutions start thinking and behaving more like for-profit institutions [104, 105].

Under this scenario, there is a need to think of new models for affordable cancer drugs. Large pharmaceutical companies can donate part of their profits to transparent international public funds created (not to their own foundations to deduct taxes, nor to the large philanthrocapitalist organizations with hidden interests). These funds can solve the most common problems of humanity, including cancer treatments. Due to their social nature, they cannot be patented and made available to all countries. At the local level, in many countries, there is no technical or financial impediment for the government to participate in the drug development process. There is an urgent need to return a medicine to the control of the public trust. The above, and the generation of many other proposals, is a moral and ethical imperative since, in the current global regime, the poorest patients in the world, those who pay their life savings for cancer treatment that will not necessarily save their life, are excluded from the medical market. During the transition to any potential solution, it is necessary to continue therapeutic repurposing in cancer and any disease. Some of the required changes are the political will of governments to engage in repurposing and legislating so that limiting intellectual property according to international treaties is not an obstacle to investing in the development of candidates to reposition. Once developed, it is imperative to legislate to adopt their use either on- or off-label according to treatment guidelines set by oncologists, absolutely devoid of industry ties [106]. We must eliminate the repeated statement that the pharmaceutical industry will not innovate without economic incentives and that, as a consequence, no one other than the pharma industry can innovate.

13 Conclusions

Despite being widely preconized as a faster, safer, and cheaper model for having anticancer drugs affordable for the population, therapeutic repurposing appears to be indistinguishable from the classic NME development model in terms of marketing aspects. This occurs at least partly because health is the way to profit and is not the pharmaceutical industry's ultimate goal. The pricing of cancer drugs is a complex issue that varies from country to country. Many alternatives have been put forward; however, these measures have thus far failed and are, at best, palliative to gaining access to cancer medicines for needy patients. There are no immediate solutions to the problem of access to cancer drugs. It is necessary to critically analyze the free market's impact on cancer care and be creative in implementing new models that genuinely benefit society.

Declarations

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