Drug repurposing in malignant pleural mesothelioma: a breath of fresh air?

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Drug repurposing is an interesting research area for mesothelioma, which has a very poor outcome and few drugs approved http://ow.ly/igTq30hSloC

Cite this article as: Boyer A, Pasquier E, Tomasini P, *et al*. Drug repurposing in malignant pleural mesothelioma: a breath of fresh air?. *Eur Respir Rev* 2018; 27: 170098 [https://doi.org/10.1183/16000617.0098-2017].

ABSTRACT Drug repurposing is the use of known drugs for new indications. Malignant pleural mesothelioma (MPM) is a rare cancer with a poor prognosis. So far, few treatments have been approved in this disease. However, its incidence is expected to increase significantly, particularly in developing countries. Consequently, drug repurposing appears as an attractive strategy for drug development in MPM, since the known pharmacology and safety profile based on previous approvals of repurposed drugs allows for faster time-to-market for patients and lower treatment cost. This is critical in low- and middle-income countries where access to expensive drugs is limited. This review assesses the published preclinical and clinical data about drug repurposing in MPM.

In this review, we identified 11 therapeutic classes that could be repositioned in mesothelioma. Most of these treatments have been evaluated *in vitro*, half have been evaluated *in vivo* in animal models of MPM and only three (*i.e.* valproate, thalidomide and zoledronic acid) have been investigated in clinical trials, with limited benefits so far. Efforts could be coordinated to pursue further investigations and test promising drugs identified in preclinical experiments in appropriately designed clinical trials.

Received: Aug 28 2017 | Accepted after revision: Jan 13 2018

Provenance: Submitted article, peer reviewed.

Conflict of interest: E. Pasquier reports personal fees for consultancy from Pierre Fabre Oncology, outside the submitted work. J. Ciccolini reports personal fees from Pierre Fabre (who commercialised a drug used in mesothelium patients), outside the submitted work. L. Greillier reports grants, personal fees and non-financial support from Roche and Novartis. He also reports personal fees and non-financial support from Lilly, Boehringer Ingelheim, AstraZeneca and Pfizer, and personal fees from Bristol-Myers Squibb, outside the submitted work. N. Andre reports personal fees and non-financial support from Bristol-Myers Squibb and Pierre Fabre for drug trials. F. Barlesi reports personal fees from AstraZeneca, Bristol-Myers Squibb, Boehringer Ingelheim, Clovis Oncology, Eli Lilly Oncology, F. Hoffmann–La Roche Ltd, Novartis, Merck, MSD, Pierre Fabre and Pfizer, outside the submitted work. C. Mascaux reports board member and speakers fees from Roche and Kephren, and speakers fees from Bristol-Myers Squibb, Lilly, Roche, AstraZeneca and Boerhingher Ingelheim, outside the submitted work.

The concept of drug repurposing

The aim of drug repurposing is to identify and develop new indications for approved drugs [1, 2]. In oncology, drug repositioning consists of demonstrating the anticancer properties of marketed drugs approved for nonmalignant diseases [3]. Because repositioned drugs have well-known safety and pharmacokinetic profiles, faster development can be expected. Indeed, clinical development can start directly with phase II trials to assess the efficacy of the drug. Furthermore, this strategy is economically attractive, particularly in low- and middle-income countries (LMIC) where accessing new cancer treatments is difficult [4]. Because it is based on old and inexpensive drugs and because most of these treatments have oral formulations, this strategy limits the need for extended hospital stays and long journeys to care centres. In addition, these drugs are known to have tolerable side-effects as compared to classical anticancer agents, so the need for supportive care is limited.

Drug repurposing relies on two main approaches: 1) activity-based repurposing, where candidate drugs are evaluated in cancer models *in vitro* and/or *in vivo* and 2) *in silico* drug repurposing, where interactions between drugs and their potential molecular targets are modelled *in silico* by using public databases and bioinformatics tools [5]. By using either or both of these approaches, several drugs approved for nonmalignant diseases have been shown to exert potent anticancer effects and have been successfully repurposed to target specific pathways. For instance, anti-angiogenic activity can be obtained with β-blockers [6] or celecoxib [7], and inhibition of the sonic hedgehog pathway can be obtained with itraconazole [8].

Potential of drug repurposing in malignant pleural mesothelioma

Malignant pleural mesothelioma (MPM) is a rare cancer with a dismal prognosis [9], mainly caused by exposure to asbestos with an aetiological fraction of ⩾80% [10]. MPM is classified into three major histological subtypes: epithelioid (50% of cases), sarcomatoid (15% of cases) and biphasic or mixed (35% of cases). MPM has a strong male predominance and is usually diagnosed 30–40 years after the occupational exposure [11]. The World Health Organization (WHO) has recognised that asbestos is one of the most important occupational carcinogens and has declared that asbestos-related diseases should be eliminated throughout the world [12]. Driscoll *et al.* [13] estimated that 43 000 people worldwide die of MPM each year, with 17 062 deaths in United States between 1994 and 2008 and 49 779 deaths in the same period in Europe [14]. The number of MPM deaths reported and the number of countries reporting MPM deaths increased between 1994 and 2008, mainly in developed countries, probably due to better disease recognition and an increase in incidence. In Europe, La Vecchia *et al.* [15] predicted that peak mortality from MPM will occur between 2010 and 2020 when the generation born between 1940 and 1950 will reach the peak age for MPM incidence and mortality. Currently, the number of MPM deaths is lower in developing countries, because developing countries began their asbestos use later [16], and because MPM is underdiagnosed as it requires expertise and immunohistochemical staining. Although asbestos production has decreased worldwide since the early 1990s because it has been banned in several countries, its use has increased in many countries as China, India, Kazakhstan, Russia, Ukraine and Uzbekistan [17]. The WHO estimates that 125 million people worldwide are still exposed to asbestos in their workplace [18]. Nowadays, asbestos exposure is high in developing countries. For example, it is reported that in India in 1994 [19], levels of fibres per cubic centimetre were found to be 100- to 1000-fold higher in textile factories or cement mills than the current permissible exposure limit in the United States. Consequently, developing countries should expect a significant rise in MPM incidence in the coming decades.

Most patients diagnosed with MPM have unresectable disease and are thus treated with chemotherapy. The standard first-line treatment for patients with advanced MPM consists in a combination of pemetrexed and cisplatin, which increases median overall survival (OS) from 9.3 to 12.1 months compared with treatment with cisplatin alone (p=0.020) [20]. Recently, the Mesothelioma Avastin Cisplatin Pemetrexed Study (MAPS) trial showed that the addition of bevacizumab to cisplatin and pemetrexed significantly increased OS (median 18.8 *versus* 16.1 months, hazard ratio (HR) 0.77 (95% CI 0.62–0.95); p=0.0167) in MPM with expected and manageable toxic effects [21]. Thereby, the cisplatin/pemetrexed/bevacizumab regimen could become a treatment option in the future for patients who are eligible to receive bevacizumab [22]. For subsequent therapy lines, no standard salvage therapy exists [23]. In a phase III trial comparing pemetrexed to palliative care alone, Sørensen *et al.* [24] demonstrated that pemetrexed improved progression-free survival (PFS) and time to progression without impact on OS. Other chemotherapeutic agents, such as gemcitabine or vinorelbine show only marginal response rates [25, 26]. Other research strategies are currently being investigated, with promising results for immune checkpoint inhibitors or antimesothelin antibodies [27, 28]. However, their high cost could limit their use in developing countries once approved.

Thus, the prognosis of patients with MPM is very poor, with an average OS of 18 months from diagnosis. Moreover, there are only few treatment options available with only one chemotherapy regimen approved

for first-line treatment of MPM and no standard treatment for second-line treatment. Thus, new treatment strategies are urgently needed. Because MPM is a rare cancer, clinical development of new drugs is difficult and requires worldwide collaboration from clinical trial centres in order to recruit more quickly and allow faster access to innovative molecules. Drug repositioning may be an attractive strategy in this pathology because it offers the possibility of faster drug development and consequently shorter paths to clinical approval. Furthermore, with the expected increase of incidence of MPM in LMIC, drug repositioning could offer solutions for patients living in these countries. Herein, we review the reported preclinical and clinical reported data of drug repurposing strategies in MPM.

Methods

We searched and extracted eligible studies about drug repurposing in MPM by an electronic search from the PubMed database. The keywords applied in the search were as follows: "mesothelioma" with "drug repositioning" or "[name of the molecule known to have an anticancer effect]". In the latter case, the molecules were selected on the basis of previous articles on drug repurposing in oncology. We selected only publications written in the English language. The manual selection of relevant trials was first based on abstract analysis. The search ended in November 2016. The bibliographies noted in all the identified studies were used to complete this search.

Antiemetic drugs

Thalidomide is a historical example of drug repositioning. The drug was first developed in the 1950s to treat morning sickness in pregnant women. This was one of the biggest man-made medical disasters: >10 000 children were born with a range of severe and debilitating malformations [29]. Thalidomide was withdrawn from the market as an antiemetic drug in the 1960s. It has since evolved to treat the cutaneous manifestations of erythema nodosum leprosum [30] and has shown antineoplastic properties by the inhibition of tumour angiogenesis [31] and cell proliferation [32], and through immunomodulatory effects [33]. Thalidomide has been evaluated in a variety of human cancers in clinical trials, which has led to its approval for the treatment of multiple myeloma [34]. In France, thalidomide is approved for previously untreated elderly patients with multiple myeloma in combination with melphalan and prednisone [35].

In MPM, thalidomide has been assessed in clinical trials without prior investigations in preclinical models. Despite encouraging results in a phase II trial with 28% disease stabilisation at 6 months observed with thalidomide as single agent in previously treated MPM patients [36], thalidomide failed to improve OS or PFS *versus* active supportive care in patients with MPM after first-line therapy in a randomised phase III study [37]. Median overall survival was 10.6 months in the thalidomide group and 12.9 months in the active supportive care group (HR 1.2, p=0.21). Similar disappointing results were observed in stage 3 nonsmall cell lung cancer (NSCLC) [38]. Table 1 provides a summary of the repurposed drugs.

Histone deacetylase inhibitors

Histone deacetylase (HDAC) inhibitors have antitumor effects by epigenetic induction of gene transcription resulting in tumour cell growth inhibition and apoptosis [39]. The first HDAC inhibitor tested in MPM was vorinostat, a HDAC inhibitor currently approved for the treatment of relapsed and refractory cutaneous T-cell lymphoma [97]. Despite encouraging *in vitro* and *in vivo* data, results in patients with MPM were disappointing, as vorinostat did not improve OS when compared to placebo in second-line or third-line therapy: median OS was 30.7 weeks in the vorinostat group and 27.1 weeks in the placebo group (HR 0.98, p=0.86) [23].

Valproate is a widely prescribed antiepileptic drug that has anticancer effect by its HDAC inhibiting properties. Among its multifaceted anticancer effects, valproate can induce tumour differentiation, reduce tumour growth and metastasis formation [98], induce apoptotic cell death [99], and increase tumour cell sensitivity to radiation [100]. Valproate showed anticancer activity in several tumour sites including glioblastoma, neuroblastoma, retinoblastoma and cervical cancer [101–103]. However, results are disappointing in myelodysplastic syndrome and acute myeloid leukaemia [104]. Valproate has shown preclinical and clinical activity in MPM. The association of valproate with pemetrexed and cisplatin increases caspase-dependent apoptosis in M14K, M38K and ZL34 human MPM cell lines, belonging to the epithelioid, biphasic and sarcomatoid subtypes, respectively and its efficacy was superior to suberoylanilide hydroxamic acid, a well-known HDAC inhibitor [105]. The synergistic activity of valproate in combination with chemotherapy was confirmed *in vivo* in mouse models of epithelioid MPM [105]. Subsequently, valproate was tested in combination with doxorubicin in patients with refractory or recurrent MPM after standard first-line chemotherapy in a phase II trial. Among 45 heavily pretreated patients, seven (16%) obtained a partial response. The median PFS was 2.5 months and the median OS was 6.7 months [40].

TABLE 1 Drugs repurposed in malignant pleural mesothelioma (MPM)

	Original indication	Anticancer effect	Advancement in oncology	Advancement in MPM
Valproate	Epilepsy	HDAC [39]	Phase II ongoing in different types of cancer	Phase II [40]
Statins	Dyslipidaemia [38]	Induction of cell cycle arrest [41] Induction of apoptosis [42] Sensitises cells to chemotherapy [43] Inhibition of angiogenesis [44] Inhibition of invasion and metastasis [45] Induction of tumour differentiation [46] Reversion of multidrug resistance [47]	Phase III: gastric cancer [48], colorectal cancer [49] Phase III: ongoing in SCLC [50]	Preclinical [47, 51–53]
Itraconazole	Antifungal	Induction of angiogenesis [54] Inhibition of hedgehog pathway [8]	Phase II: NSCLC [55] Prostate cancer [56] Basal cell carcinoma [57]	Preclinical [58]
Arsenic trioxide	Traditional Chinese medicine	Induction of apoptosis [59]	FDA approved: promyelocytic leukaemia [60] Phase III: hepatocellular carcinoma	Preclinical [58, 61, 62]
Disulfiram	Addiction to alcohol [63]	DNA N-methyl transferase inhibition	Phase II: NSCLC [64]	Preclinical [65]
Celecoxib	NSAIDs [66]	Inhibition of cell cycle progression [67] Inhibition of apoptosis [68] Inhibition of angiogenesis [69]	Phase II: breast cancer [70], glioblastoma [71], ovarian cancer [72] Phase III: ongoing in different types of cancer	Preclinical [73]
Metformin	Diabetes type 2	Inhibition of mTor [74] Inhibition of cell cycle [75] Inhibition of EMT [76]	Phase II: pancreatic cancer [77] Phase III ongoing: breast cancer [78], endometrial cancer [79]	Preclinical [80]
Tocotrienol	Antioxidant [81, 82]	Inhibition of angiogenesis [83] Inhibition of PI3K/AKT pathway [84] Reversion of chemoresistance [85]	Phase II: breast cancer [86] Phase II ongoing: ovarian cancer [87]	Preclinical [52, 85, 88]
Thalidomide	Sickness in pregnant females (withdrawn) [29]	Inhibition of angiogenesis [31] Inhibition of cell proliferation [32] Immunomodulatory function [33]	FDA approved: multiple myeloma [34]	Phase III [37]
Anisomycin	Antibiotic	Induction of apoptosis [89]	Preclinical [90]	Preclinical [90]
Zoledronic acid	Osteoporosis, hypercalcaemia [91]	Inhibition of cell proliferation Inhibition of invasion Inhibition of angiogenesis Inhibition of bone metastases Immunomodulatory function [92, 93] Reversion of chemoresistance [94]	Phase III: breast cancer [95]	Phase II [96]

HDAC: histone deacetylase inhibitor; SCLC: small cell lung cancer; NSCLC: nonsmall cell lung cancer; FDA: United States Food and Drug Administration; NSAIDs: nonsteroidal anti-inflammatory drugs; EMT: epithelial–mesenchymal transition.

Statins

Statins are a class of drugs with lipid-lowering effect through inhibition of the mevalonate pathway [106]. Statins have antineoplastic properties [107] such as cell cycle arrest [41], apoptosis induction [42], sensitisation to cytotoxic drugs [43], angiogenesis inhibition [44], invasion and metastasis inhibition [45] and tumour differentiation [46]. In a recent retrospective study in small cell lung cancer, a statistically significant increase in median OS was observed in statin-treated patients when compared to those not receiving statins (median OS 8.4 *versus* 6.1 months, $p<0.05$) [105]. Results from a phase III comparing etoposide and cisplatin or carboplatin as first-line chemotherapy with or without pravastatin in preteated patients with small cell lung cancer are expected [50]. In a phase III clinical trial, statins failed to improve OS in gastric cancer patients in combination with capecitabine [48] or in colorectal cancer patients in combination with Xeliri/Folfiri [49].

Statins have been extensively investigated *in vitro* in human MPM cells. Lovastatin [109] was shown to decrease cell viability in a dose-dependent manner in human MPM cell lines, through apoptosis induction. In addition, the combination of lovastatin and valproate was shown to reduce cell invasion of Acc-Meso-1, a human-derived MPM cell line [110]. Hwang *et al.* [51] reported a synergistic effect of the combination of pemetrexed and simvastatin on apoptosis induction in MSTO-211 MPM cells by reactive oxygen

species-dependent mitochondrial dysfunction and Bim induction. Riganti *et al.* [47] showed that statins revert doxorubicin resistance by increasing nitric oxide production in human MPM cells MM98, OC99 and GF99. Additionally, statins have been shown to exert synergistic antiproliferative effects with γ-tocotrienol (isoform of vitamin E) on human MPM cells H2052 (sarcomatoid), H28 (epithelioid), H2452 (biphasic) and MSTO-211H (biphasic; MSTO) *via* inhibition of the mevalonate pathway, induction of endoplasmic reticulum stress and caspase 3 activation [52]. The potential of lovastatin alone has also been demonstrated *in vivo* as it significantly reduced primary tumour and metastasis in a NOD/SCID/γ-null (NOG) mouse model of human MPM [53]. The role of statins in MPM has not yet been investigated in clinical trials.

Antifungal drugs

Itraconazole is an antifungal drug with several proven antiproliferative properties. Itraconazole acts as an anti-angiogenic agent [54] by direct inhibition of vascular endothelial growth factor receptor (VEGFR)2 glycosylation and consequently inhibits VEGFR2 autophosphorylation after VEGF stimulation [111]. It also inhibits the hedgehog signalling [8] pathway by acting on the smoothened protein (an essential hedgehog pathway component) and consequently suppressing the tumour growth. Of note, hedgehog signalling is involved in MPM cell growth [112]. Itraconazole has shown encouraging results in phase II trials in several tumour types. In previously treated NSCLC, itraconazole combined with pemetrexed was superior compared to pemetrexed alone (median OS 32 months *versus* 8 months, p=0.012) [55]. In addition, itraconazole showed activity in castration-resistant metastatic prostate cancer [56] and in basal cell carcinoma [57].

Furthermore, itraconazole [58] suppresses the viability of various human MPM cell lines of epithelioid, sarcomatoid and biphasic subtypes, in a dose-dependent manner, at least in part by reducing Gli1 expression, which is a key actor of the hedgehog pathway. However, itraconazole is yet to be evaluated *in vivo* or in a clinical trial in MPM.

Traditional Chinese medicine

Traditional Chinese medicine relies in part on the concept of using a controlled dose of poison to treat patients [113]. Arsenic trioxide (ATO) is an inorganic compound, which has been used in traditional Chinese medicine [61] to treat a wide variety of illnesses including syphilis and parasite infections. ATO has been repositioned successfully in oncology. It exerts its anticancer effects through the induction of apoptosis [59], and the inhibition of angiogenesis by inhibiting VEGF-A expression [114]. ATO has been approved by the United States Food and Drug Administration (FDA) since 2000 for patients with relapsed promyelocytic leukaemia [60]. In addition, ATO has been assessed in solid tumours with encouraging results in hepatocellular carcinoma [115] when combined to locoregional therapy (overall response rate 81.96% (95% CI 72.32–91.62%) *versus* 59.37% (95% CI 47.34–71.41%) for patients treated by locoregional therapy alone; p<0.05). Although ATO was approved by the FDA when administered intravenously, oral formulations have been developed and have shown activity equal to the intravenous formulation, and a more favourable toxicity profile [60].

The effects of ATO on human MPM cells have been assessed *in vitro*. Like itraconazole, ATO suppresses cell viability of various MPM cell lines by reducing [58] Gli1 expression. In addition, ATO was shown to induce apoptosis in the NCI-H2052 MPM cell line [61] by activating two mitogen-activated protein kinase pathways: the c-Jun NH2-terminal kinase pathway and the response and extracellular signal-regulated kinase (ERK) pathway. The ERK pathway mediates cell proliferation and apoptosis [116]. An antiproliferative effect and cytotoxic effect of ATO [62] was also reported in multiple MPM cell lines (sarcomatoid, epithelioid and biphasic) by apoptosis induction mediated through downregulation of E2F1, a transcription factor involved in proliferation, apoptosis, cell cycle, tumour growth and senescence [117], and downregulation of thymidylate synthase, which is involved in pemetrexed resistance when overexpressed [118].

The role of ATO on human MPM was confirmed *in vivo* [62] using a nude mouse xenograft model of epithelioid MPM. The relative tumour size after 23 days of ATO treatment was statistically lower comparing to control group (p<0.05) with suppression of E2F1 expression and caspase-3 cleavage. ATO has not been tested in MPM patients yet.

DNA methyltransferase inhibitors

Disulfiram (DSF), a member of the dithiocarbamate family, is an irreversible inhibitor of aldehyde dehydrogenase approved by the FDA to treat alcoholism [63]. DSF inhibits tumour growth by its epigenetic properties as a DNA methyltransferase inhibitor [119]. In addition, DSF can potentiate the effects of anticancer drugs [120, 121]. In a recent phase II trial, the addition of DSF to cisplatin and

vinorelbine [64] was found to increase OS in NSCLC patients as compared with chemotherapy alone (10 *versus* 7.1 months, p=0.041). Moreover, there were two long-term survivors in the DSF group.

DSF has been assessed *in vitro* in human MPM *via* a DSF–copper (DSF-Cu) complex, as copper is required in DSF-induced toxicity and radio sensitisation of cancer cells [122]. The complex DSF-Cu inhibits proliferation of MPM cell lines *via* promotion of apoptosis, in part by inhibiting nuclear factor-κB in a dose-dependent manner [65]. The inhibition growth tumour by stimulating apoptosis was confirmed *in vivo* [65]. DSF-Cu-treated Balb/c mice xenografted with MPM AB12 murine cells showed a 71% inhibition of tumour growth compared to control tumours. As previously seen *in vitro*, DSF-Cu inhibited murine MPM tumour growth by promoting apoptosis.

Nonsteroidal anti-inflammatory drugs

Acetylsalicylic acid or aspirin inhibits cyclooxygenase (COX)-1 and COX-2 and is the most widely used nonsteroidal anti-inflammatory drug worldwide [123]. Aspirin has been shown to induce apoptosis in both COX-dependent and COX-independent mechanisms [124], and suppresses the acquisition of chemoresistance [125]. The use of aspirin has demonstrated improved outcomes in colorectal cancer [126, 127].

Aspirin [115] was shown to inhibit colony formation in REN, HMESO and PHI, three MPM cell lines secreting high amounts of high-mobility group box (HMGB)1, a protein that regulates nucleosome assembly and chromatin structure. In contrast, aspirin does not inhibit colony formation in the PPM-MILL cell line, which secretes low-to-undetectable amounts of HMGB1. Moreover, motility, migration, invasion and epithelial–mesenchymal transition (EMT) of REN cells was inhibited by aspirin in a HMGB1-dependent manner. The anticancer and HMGB1-inhibiting activity of aspirin on MPM cells was confirmed *in vivo* [123]. Severe combined immunodeficient mice (SCID) were xenografted with HMGB1-secreting REN cells (derived from an explant of an epithelial MPM) and aspirin significantly reduced tumour growth compared with control (p<0.0001). Aspirin has not yet been tested in clinical trials in MPM patients.

Celecoxib is a selective COX-2 inhibitor [66] approved by the FDA since December 1999 in familial adenomatous polyposis [128]. Among its anticancer effects, celecoxib inhibits cell cycle progression [67], induces apoptosis [68], inhibits angiogenesis and metastasis [69], and increases tumour cell lysis induced by immune cells [129]. The efficacy of COX-2 inhibition by celecoxib has been assessed in phase II clinical trials of different tumours with conflicting results [70–72]. In a recent meta-analysis [130], we noted an improvement of response rate for advanced NSCLC patients when chemotherapy was associated with celecoxib compared to chemotherapy alone (odds ratio (OR) 1.34, 95% CI 1.08–1.67; p=0.009) without improvement of 1-year survival rate (OR 1.08, 95% CI 0.8–1.35; p=0.512). Several phase III trials are ongoing in different cancers. In MPM, celecoxib was shown to reduce prostaglandin E2 levels in AB1, a murine MPM cell line [73]. The impact of COX-2 inhibition by celecoxib has been evaluated *in vivo* in BALB/c mice xenografted with AB1 cells. Celecoxib reduced the number of myeloid-derived suppressor cells, which play a critical role in tumour immune escape by suppressing T-cell and natural killer cell function. Consequently, combining dendritic cells (DC)-based immunotherapy with celecoxib in MPM improved survival (p=0.027), compared to a single treatment with celecoxib (p=0.305) or DC-based immunotherapy (p=0.456). Clinical assessment of the role of COX-2 in MPM is missing.

Oral antidiabetics

Metformin is a biguanide derivative, which is prescribed for type 2 diabetes. Metformin may act as an anticancer drug through inhibition of the mTor pathway [74], cell cycle arrest leading cells to apoptosis [75] and inhibition of EMT [76]. Retrospective analyses of medical records of diabetic patients treated by metformin have suggested an improved cancer prognosis [131]. In a phase II clinical trial, there was no advantage for the addition of metformin to erlotinib and gemcitabine in the treatment of advanced pancreatic cancer, but we noted that a subgroup of patients with high plasma concentrations of metformin (>1 $mg{\cdot}L^{-1}$) seemed to have an improved survival (HR 0.37, 95% CI 0.14–0.98; p=0.049) [77]. Several phase III trials are currently ongoing, especially in breast and endometrial cancers [78, 79].

The tunnelling nanotubes are thought to be an alternative means for intercellular communication in cancer and it is possible that they propagate chemotherapy resistance *via* intercellular transfer of proteins [80]. Tunnelling nanotube formation occurs during mesothelioma cell invasion *in vitro*. In MPM, the influence of metformin on the intercellular transfer of cellular contents has been assessed in cell lines of the biphasic, sarcomatoid and epithelioid types. Metformin suppressed tunnelling nanotube formation *in vitro* [132], as did everolimus, an mTor inhibitor. Despite this effect, metformin did not significantly affect cell proliferation. To our knowledge, metformin has not been investigated *in vivo* or in clinical trials in MPM. However, a retrospective analysis [133] of 300 patients with type 2 diabetes and MPM showed no

evidence that metformin could improve survival: median OS was 8.8 months for metformin users *versus* 6.5 months for nonusers (p=0.37).

Vitamin E isoform

Tocotrienol (T3) is one of the isoforms of vitamin E which acts as an antioxidant, anti-inflammatory agent and is implicated in curing age-associated disease [81, 82]. γ-T3 and δ-T3 have the most extensively described anticancer properties [134, 135]. γ-T3 inhibits tumour angiogenesis [83] and cancer cell proliferation by acting on the PI3K/Akt pathway [84]. Tocotrienol-rich fraction (TRF) extracted from rice bran is an abundant source of γ-T3. A monocentric study has been undertaken [86] to test the effectiveness of adjuvant TRF therapy in combination with tamoxifen in women with early oestrogen receptor-positive breast cancer. However, this combination failed to improve outcome compared to tamoxifen alone. A phase II trial is ongoing in previously treated ovarian cancer patients comparing tocotrienol with cabazitaxel [87].

In vitro, Nakashima *et al.* [85] showed that the TRF extracted from rice attenuates the chemoresistance to cisplatin by inactivating the PI3K/Akt pathway in H28, a human cisplatin-resistant MPM cell line. In combination with statins, γ-T3 exerts antiproliferative effects [52] on human sarcomatoid, epithelioid and biphasic MPM cells through inhibition of the mevalonate pathway, induction of endoplasmic reticulum stress and caspase 3 activation. γ-T3 has not been investigated *in vivo* or in clinical trials in MPM.

α-tocotrienol is another isoform of tocotrienol with pro-apoptotic anticancer properties [136]. 6-O-carboxypropyl-α-tocotrienol (T3E), a redox-silent analogue of α-tocotrienol has been evaluated *in vitro* in human MPM cell lines. T3E inhibits the growth of human MPM H28 cells [88], while sparing the growth of nontumorigenic mesothelial cells (Met-5A). The inhibition of MPM cell growth was mediated by the inactivation of Stat3 and the Src family of protein tyrosine kinases (SFK). SFK is activated in MPM cell lines and is involved in cell migration and invasion [137]. T3E also inhibits HIF-2α accumulation and VEGF secretion by the inactivation of Yes, a member of SFK that has been reported to be a central mediator of cell growth in MPM [138]. α-T3 has not been investigated *in vivo* or in clinical trials in MPM.

Antibiotics

Anisomycin is an antibiotic produced by *Streptomyces griseolus*, inhibiting protein synthesis [139]. It also acts as a protein translation inhibitor known to sensitise tumour cells to apoptosis induced by TNF-related apoptosis-inducing ligand (TRAIL) [89]. In H28 and REN MPM cell lines [90], anisomycin delivered at low subtoxic concentrations (25 $ng \cdot mL^{-1}$) was a potent sensitiser of apoptosis induced by TRAIL. In contrast, anisomycin did not sensitise nonmalignant human mesothelial cells to TRAIL-induced apoptosis. This sensitisation was shown to require Bim, indicating that anisomycin sensitises MPM cells to TRAIL-induced apoptosis at the level of the mitochondria. These data have not been confirmed *in vivo* or in clinical trials.

Bisphosohonates

Bisphosphonates are currently used in clinical for decades for bone lesions such as osteoporosis, cancer-induced osteolytic bone disease and hypercalcaemia [91].

In addition to these properties, nitrogen-containing bisphosphonates such as zoledronic acid (Zol) have anticancer effects [92, 93] such as inhibition of tumour cell proliferation, inhibition of tumour cell adhesion and invasion, inhibition of angiogenesis, inhibition of bone metastases and immunomodulatory effects. The administration of Zol (and clodronate) could be an option as adjuvant therapy for postmenopausal patients with breast cancer, because the EBCTCG meta-analysis found a little benefit in postmenopausal patients by reducing the rate of breast cancer recurrence in the bone and improving breast cancer survival [95, 140]. In advanced NSCLC with bone metastases, adding Zol to chemotherapy improves OS as compared with chemotherapy alone (578 days *versus* 384 days, p<0.0001) [141]. In castration-resistant prostate cancer, Zol reduces skeletal-related events, especially when combined with docetaxel [143]. In addition, Zol has been shown to reduce skeletal-related events in multiple myeloma patients [143].

Zol has shown preclinical and clinical activity in MPM. In human mesothelioma cells 211H, H28, H226, H2052, H2452 and Met-5A, Zol suppresses the growth of mesothelioma cells through apoptosis induction and cell cycle arrest in a p53-independent manner [144]. Moreover, Wakchoure *et al.* [145] have shown that Zol inhibited the growth of AB12 and AC29 mouse mesothelioma cells by inhibiting the mevalonate pathway. Moreover, Zol was shown to decrease the Ras/ERK1/2 activity which is responsible for chemosensitising human mesothelioma cells to P-glycoprotein substrates (doxorubicin, vinblastine and etoposide) and to decrease indoleamine 1,2 dioxygenase-mediated immunosuppression [94]. The activity of Zol on mesothelioma cells was confirmed *in vivo* with inhibition of tumour growth when Zol was

administrated intrapleurally in a dose-dependent manner [144]. Zol was subsequently tested in a prospective single-arm clinical trial in patients with unresectable MPM who had progressed after one or more prior systemic therapies. Among eight pretreated patients, the median PFS was 2 months and the median OS was 7 months without significant toxicity. In this study, a decrease of VEGF level was predictive of favourable response [96].

Conclusions

Because the prognosis of patients with MPM remains poor, and with its incidence on the rise, particularly in LMIC, new and innovative research perspectives are required. This review highlights the potential of using drugs approved for nonmalignant disease, which could be investigated. Although other important research avenues are currently being investigated in MPM, such as immune checkpoint inhibitors, vaccine or antimesothelin monoclonal antibody [27, 28], drug repurposing could provide cheaper and more accessible treatment options for patients in developing countries.

Mesothelioma is a tumour with known molecular alterations [146] in different signalling pathways, for which there is not necessarily an available treatment. In this review, we attempted to draw up a comprehensive list of the various repurposed drugs that have been evaluated in mesothelioma in preclinical or clinical studies. We have tried to understand the mechanisms involved in the antitumor activity of each of them.

So far, only three repurposed drugs have been investigated in clinical trials in MPM: valproate and thalidomide showed good results in phase II trials. However, in a phase III trial thalidomide failed to improve outcomes, and valproate has not yet been tested. Two drugs with promising results in preclinical assessments failed to be confirmed as being useful in patients. This highlights that high failure rates in patient evaluations in clinical trials often occur, despite promising data at the preclinical level, and consequently, preclinical data may never be translated to patients. Thus, preclinical data should be assessed in early-phase clinical trials.

Even if drug repositioning is an attractive approach, investigators should keep in mind its limitations. The first is that the repurposed drugs are rarely effective in monotherapy, with antitumour activity more frequently seen in association with other repurposed drugs or known cytotoxic drugs. Moreover, although the low cost of these treatments may be an advantage in being able to treat a large number of patients in developing countries, this could be a barrier for pharmaceutical companies to push their indication into oncology. In addition, these molecules are currently no longer patentable and substitutes are often available, making their commercial interest very low. Finally, their use could be limited by their possible side-effects and their contraindications. Although these drugs are known to have tolerable side-effects, their toxicity in cancer patients treated with other cytotoxic drugs is not known. For example, there were two toxic deaths in 16 patients treated with valproate–doxorubicin [40].

Drug repurposing is an innovative and interesting research area, particularly in MPM where few treatments are approved and where research may be time-consuming due to a lower incidence than other types of thoracic cancer. In addition, if drug repurposing was found to be effective in clinical trials, this strategy could potentially treat a large number of patients with MPM around the world, as its incidence will mostly increase in the poorer countries, where access to innovative molecules is limited.

Thus, clinical trials evaluating this therapeutic strategy in MPM are needed. These must be conducted after selecting the most relevant drugs or drug associations in preclinical models. To fast-track selection of treatment regimens, *in silico* approaches can be used to model the interactions between drugs and their molecular targets and thus test a large number of combinations. Indeed, many signalling pathways involved in MPM are known, as are many potential targets of known drugs.

However, many questions arise about how best to conduct a clinical trial of drug repurposing in MPM. Because there is no treatment currently approved, second-line therapy appears to be the most appropriate setting. The association with pre-existing cancer treatments or the combination of multiple repurposed drugs acting on complementary signalling pathways may be more active than the monotherapy approach. In conclusion, drug repurposing is an important research area in mesothelioma, with many questions remaining unresolved on the different modalities, but a promising avenue for medical advances.

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