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Fundamentals for the repurposing of hydralazine as an anti-neoplastic drug

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Abstract

Hydralazine (HDZ) is a drug patented in 1949 that has been used for the treatment of arterial hypertension since 1953. New and better anti-hypertensive drugs have almost moved HDZ into oblivion. Interestingly, anti-cancer effects were found and this drug is seriously being considered for repurposing it for cancer treatment. The main mechanism of action against tumors seems to be its ability to act as a demethylator agent. By demethylating the promoter region of tumor suppressor genes HDZ seems to restore the effects of these genes, which are frequently inhibited in cancer through epigenetic mechanisms. However, HDZ also has some other important involved mechanisms such as anti-angiogenesis, and reversal of resistance to imatinib. Particularly important is its ability to restore the activity of non-mutated p16 in cancer. HDZ ability to inhibit glutamate oxaloacetate transaminase 1 is a recent finding that will probably add further interest to the drug in cancer treatment. This review analyzes the anti-tumoral effects of HDZ.

Keywords: Hydralazine; Cancer; Valproate; DNA methyltransferases

1. Introduction

Hydralazine (HDZ) was discovered almost by chance in 1949 when scientists at Ciba laboratories were searching for antimalarial drugs (1). This compound was used, and still is, for the treatment of arterial hypertension and heart failure (2). Although it is not marketed any longer in most countries. The anti-hypertensive effect is related to its vasodilator abilities through relaxation of arteriolar smooth muscle (3, 4), . Lowering blood pressure usually reflexively increases heart rate.

In 1980 it was found that HLZ and its derivative dihydroHDZ interacted with DNA and produced DNA damage in rat liver at concentrations used in the clinical setting, therefore that it was mutagenic and genotoxic (5). This was confirmed in human cells as well (6). This raised the possibility that HDZ could eventually increase cancer risk. Kaufman et al. found that protracted use of hydralazine did not increase the risk of breast cancer (7), but did increased the risk of colon cancer (8).

In rabbits the slow acetylators showed HDZ-related DNA damage, but this was not the case of rapid acetylators (9). Hence, the acetylator phenotype was strongly related to the possible DNA damage.

HDZ, dihydroHDZ and endralazine (the three derivatives of hydrazine) produced DNA damage, with HDZ being the least genotoxic (10).

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2. Chemistry and pharmacodynamics

HDZ is a phtalazine derivative. Fig.1. It is rapidly absorbed in the gastrointestinal tract. Although the half life in plasma is short, its clinical effects remain for much longer because the drug has high affinity for the arteriolar smooth muscle where it accumulates. The drug is partially metabolized through acetylation and the population can be distinguished in slow and quick acetylators. Slow acetylators have a tendency to show side effects.

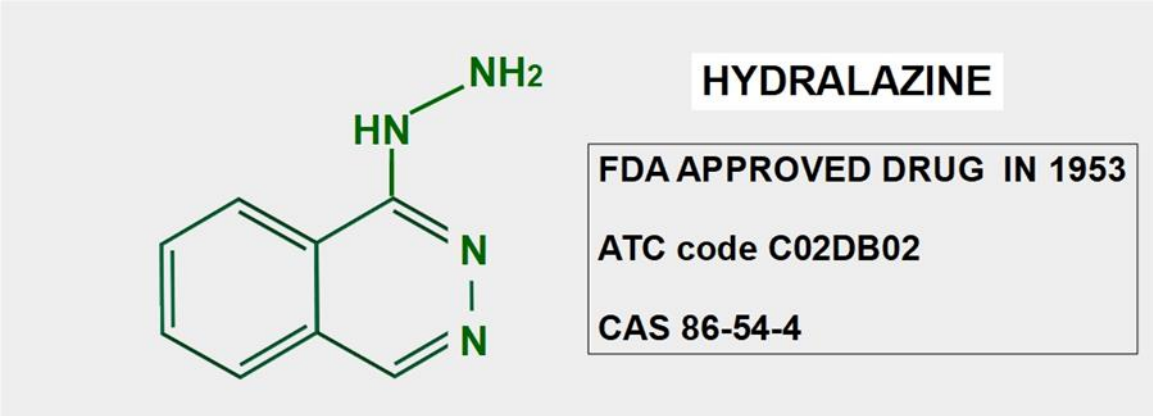

Figure 1 Chemical structure and classification of hydralazine. Hydralazine interferes with calcium transport to relax arteriolar smooth muscle and lower blood pressure. Hydralazine has a short duration of action of 2-6h.

2.1. Mechanism of action

Different mechanisms may be involved in HDZ's antitumoral effects. The best known consists of demethylation, e.g. demethylation of a tumor suppressor gene such as p16. It also re-expressed the estrogen receptor gene and the retinoic acid receptor genes. Importantly, HDZ was tested in xenografted mice and in two patients (11). It was found that the re-expressed genes became functional. The authors treated two cancer patients with hydralazine for 10 days and found that hydralazine demethylated and re-expressed the p16 gene in the head and neck cancer patient and the RAR gene in the cervical cancer patient. The dose used was slightly inferior to the maximum used for hypertension treatment (200 mg daily). Procainamide showed similar results. Unfortunately, there is no further information about the patients` outcome. The main anti-tumoral effect seems related to its activity as a demethylating agent through inhibition of DNA methyltransferases (12). Docking studies have shown that HDZ seems to interact similarly with DNA methyltransferases as other inhibitors such as deoxycytidin analogs (13).

Tang et al.(14) were able to restore the activity of ERα receptors in non-expressing human breast cancer cells with HDZ. In these cells, they observed that increased methylation of the receptor`s promoter region was related to tumor progression.

The association of HDZ with valproate (an histone deacetylase inhibitor) has shown synergistic epigenomic effects (15, 16). A clinical phase III trial of HDZ plus valproate and classic chemotherapeutics in advanced cervical cancer showed encouraging results (17). This association also radio-sensitized cervical cancer cells (18). Similar promising results were found in a phase I clinical trial for breast cancer, in which hydralazine plus valproate were associated with doxorubicin and cyclophosphamide (19).

HDZ + valproate were able to reverse chemoresistance in 80% of a small group of patients with solid tumors in a phase II clinical trial(20).

In castration-resistant prostate cancer cells HDZ acted synergistically with enzalutamide (21).

Although the HDZ-valproate association produced apoptosis in cutaneous T-cell lymphoma cells, the association of vorinostat with decitabine seemed superior (22).

TRANSKRIP is an extended-release hydralazine hydrochloride and magnesium valproate with distinctive specificity for each patient's type of rapid or slow acetylation. TRANSKRIP is a dual antitumor agent included and classified within the framework of so-called epigenetic therapies, which are directed against molecular targets. It is the first representative epigenetic therapy agent that individually combines hydralazine hydrochloride, an inhibitor of DNA methyltransferases,

with magnesium valproate, an inhibitor of histone deacetylases. These two enzymes are crucial for the development and progression of cancer as well as for resistance to treatment; since DNA hypermethylation and histone deacetylation turn off the expression of tumor suppressor genes (23). Only in Mexico is it approved for the treatment of metastatic, recurrent, or persistent cervical cancer in association with standard chemotherapy.

In 2022, Wu et al.(24) found another anti-tumoral mechanism: HDZ is an inhibitor of Glutamate oxaloacetate transaminase 1 (GOT1). This enzyme is an aspartate aminotransferase. It has pro- and anti-tumoral effects with the first being predominant.

When inhibited it promotes pancreatic cancer ferroptosis (25), while uninhibited it prevents pancreatic cancer cell death and promotes its progression (26). It was found that KRAS- mutated cancer cells rely heavily on GOT1 for long-term proliferation, and GOT1 inhibition sensitizes the malignant cells to glucose deprivation (27). Therefore, discovering HDZs abilities to inhibit this enzyme is an important finding that gives a new perspective on this drug.

Dehghan et al. (28) found that HDZ increases mitochondrial activity in C. elegans by targeting cAMP-dependent protein kinase which activates sirtuin 1/5. Figure 2

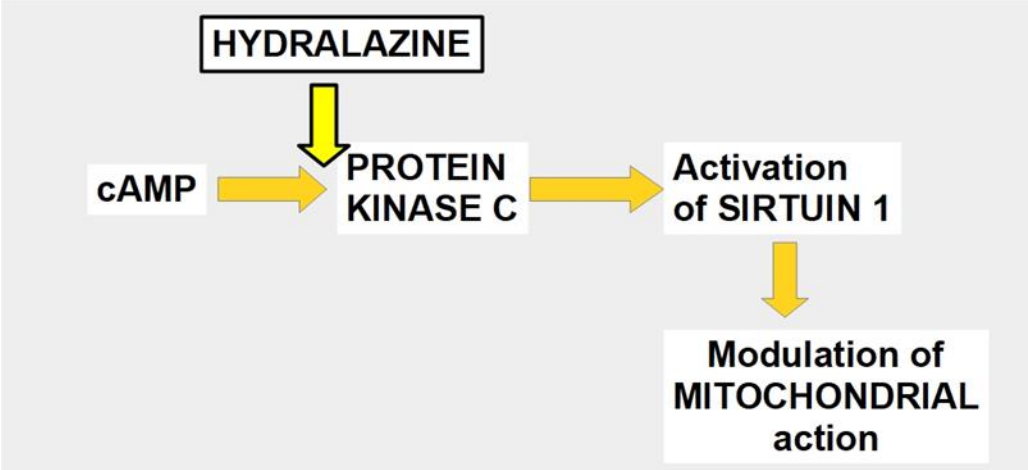

Figure 2 The influence of this mitochondrial modulation has not been tested in human cells, and its importance in cancer has not been investigated yet.

2.2. List of registered clinical trials for hydralazine in cancer

There are only 7 ongoing or completed registered clinical trials for hydralacine in cancer: one in the USA and the rest in Mexico.

- **NCT00996060** Use of Hydralazine and Valproic Acid in Advanced Solid Tumor Malignancies. Lung cancer Phase I.
- **NCT00404508** A Phase II Study of Epigenetic Therapy to Overcome Resistance in Refractory solid tumors
- **NCT00533299**Hydralazine Valproate for Ovarian Cancer
- **NCT00532818**Hydralazine Valproate for Cervical Cancer
- **NCT02446652** Evaluation of TRANSKRIP ® Plus Chemotherapy in Recurrent-Persistent Cervical Cancer
- **NCT00404326** Hydralazine and Valproate Plus Cisplatin Chemoradiation in Cervical Cancer
- **NCT00395655** Hydralazine and Valproate Added to Chemotherapy for Breast Cancer

Table 1 A summary of further evidence on HDZ anti-cancer effects

Reference	Findings
Yung et al. 2022 (29)	In a large population study of patients with chronic administration of HDZ or valproate, a small reduction in the risk of hematological malignancies was found.
Liu et al. 2022 (30)	An association of HDZ, valproate, gemcitabine and cisplatin followed by dacarcazine and doxorubicin, were used to treat chemo-naive patients with advanced hepatocellular carcinoma. The median overall survival was 14.6 months. The response rate was 27%. The conclusions of the authors were that valproate and HDZ combined sequential therapy was effective with manageable toxicities.
Pacheco et al. 2021 (31)	Prostate cancer cells LNCaP, 22Rv1, DU145 and PC-3 were exposed to HDZ, valproate and panobinostat (an HDAC inhibitor). All three independently reduced viability of all the prostate cancer cell lines tested. When used in association they showed synergy.
Kumanishi et al. 2019 (32)	Synergy was found between vascular endothelial growth inhibitor and the association HDZ + valproic acid association in human osteosarcoma cell lines.
Chen et al. 2019 (33)	HDZ significantly increased nanoparticle penetration in advanced desmoplastic tumors. This should represent a new way to improve treatments for pancreatic cancer and desmoplastic melanoma.
Perez-Cardenas et al. 2018 (34)	Treating Ras-transformed NIH 3T3 cells with HDZ + valproate they found growth-inhibitory effects, inhibited cell motility and decreased expression of Ras. In vivo there was an important decrease of lung metastasis.
Espinoza-Zamora et al. 2017 (35)	In a phase II clinical trial the hydralazine and valproate (Transkrip) association, was found to be useful for the treatment of refractory and progressive cutaneous T-cell lymphoma.
Ruiz Magaña et al. 2016 (36)	It was found that HDZ induced caspase-dependent apoptosis in human p53-mutant leukemic T cells.
Graça et al. 2014 (37)	*In vitro* they showed that hydralazine induced a significant dose and time-dependent growth inhibition, increased apoptosis, decreased invasiveness and induced cell cycle arrest in DU145 prostate cancer cells. HDZ restored androgen receptor expression with upregulation of its target p21.
Bauman et al. 2014 (38)	A group of patients with advanced non-resectable solid tumors previously treated with heavy chemotherapy received high doses of HDZ and usual doses of valproate. One partial response and 5 stable disease were observed among the 26 patients.
Candelaria et al. 2012 (39)	In gemcitabine-resistant cervix cancer cells the authors found down-regulation of hENT1 and dCK genes independent of promoter methylation. Treatment with HDZ reversed resistance and increased the expression of the hENT1 and DCK genes through inhibition of G9A histone methyltransferase
Yamanegi et al. 2012 (40)	Valproate and HDZ increase the susceptibility of osteosarcoma cells to Fas- and NK cell-mediated cell death. When used in association these effects were further enhanced .
Jiang et al. 2011 (41)	HDZ associated with thiazolidinedione suppressed proliferation and induced apoptosis in triple negative breast cancer MDA-MB231 cells by increasing the expression of PPARγ. HDZ by itself increased the expression of PPARγ in vitro and in vivo.
Cruz-Hernandez et al. 2011 (42)	Seven-day treatment with HDZ plus valproate increased the expression of 964 genes in patients. The oxidative phosphorylation pathway genes were among the more expressed in cervical cancer patients. p53 was also up-regulated.
Dueñas-Gonzalez et al. 2010 (43)	A patient with micosis fungoide showed a very important favorable response with the association HDZ-valproate.
Song et al. 2009 (44)	HDZ induced expression of the APC gene in HeLa and CaSki cervix cancer cells, and inhibited growth in approximately 50% and increased apoptosis.

Segura-Pacheco et al. 2006 (45)	The authors showed that DNA hypermethylation was a participant in the multidrug-resistant phenotype in the MCF-7 breast cancer cells resistant to adriamycin. HDZ could reverse resistance.
Mora-Garcia, et al. 2006 (46)	Valproic acid and HDZ up-regulated the constitutive HLA class-I expression in spite of constitutive promoter demethylation in cervix cancer cells.
Zambrano et al. 2005 (47)	Phase I clinical trial of HDZ. All the patients had at least one methylated gene. Genes (APC, MGMT; ER, GSTP1, DAPK, RARβ, FHIT and p16) were studied pre and post-treatment. Approximately the gene was re-expressed in 75% of the cases.
Bibby et al. 1993 (48)	HDZ increased cytotoxicity on malignant cells of the experimental chemotherapeutic drug EO9 (apaziquone which is related to mitomycin).
Siemann 1990 (49)	HDZ administered after the chemotherapeutic drugs melphalan, cyclophosphamide or CCNU, increased the extent of apoptosis in sarcoma and RIF-1 tumor.
Chaplin, 1989 (50)	Hydralazine increased the effects of chemotherapeutic drugs on the tumor. The author thought that this was due to increased hypoxia.
Adams et al. 1989 (51)	Melphalan induced growth delay was increased 2.5 fold with previous administration of HDZ.
Chaplin et al. 1987 (52)	HDZ increased the cytotoxicity of cytotoxin RSU 1069 in mice bearing Lewis lung tumors.

2.3. Is hydralazine a pro-angiogenic or anti-angiogenic drug?

HDZ has shown abilities to reduce angiogenesis in vitro and in vivo (53). It inhibited HUVEC proliferation, wound healing, migration, and tube formation of endothelial cells. The secretion of VEGF and bFGF were reduced as well. However, this is a contradictory issue because it has been shown that HDZ targets prolyl hydroxylase and increases HIF-1α expression which in turn induces VEGF expression increasing blood vessels density (54). The strong evidence supporting HDZ`s hypoxic effects (55) makes us believe that it is pro-angiogenic. The origin of this controversy may be due to a different effect of hydralazine in spontaneous and transplanted tumors (56). Another confounding factor is that hydralazine significantly lowers blood pressure in experimental animals, particularly in mice, leading to ischemia in some organs (57).

2.4. Hydralazine decreases blood flow in tumors and causes hypoxia

Injecting HDZ into arteries of rats reduced blood flow in most normal tissues. However, this significant reduction was much more important in xenografted tumors (58). This tumor- hypoxic effect was also found by other authors (59-63). However, low concentrations of HDZ increased blood flow while larger concentrations had the opposite effect (64). The reduction of blood flow in hepatocarcinoma by HDZ led to the development of an improved mechanism to detect the tumor with ultrasound studies and distinguish tumors from cirrhosis (65).

2.5. Hydralazine in the reversal of imatinib resistance in chronic myeloid leukemia

Eight patients with chronic myeloid leukemia resistant to imatinib were treated with HDZ associated with valproate and continued imatinib treatment: two patients were suffering a blastic reaction, other 5 in a progressive phase and one with a chronic phase. Only one patient failed to improve. Two patients underwent a complete cytogenetic response, three achieved stable disease and other two had partial cytogenetic response. They were followed for 18 months and the median survival was not reached (66).

2.6. Hydralazine in the treatment of polycithemia vera

HDZ allowed a significant reduction in phlebotomies as part of the treatment of patients with polycithemia vera (67).

2.7. Hydralazine as a resistance-preventive drug

In rats with breast tumors hydralazine associated with valproate prevented tamoxifen resistance and prevented tumor recurrence, compared with controls (68).

2.8. Hydralazine and intracellular pH

Nigericin lowers intracellular pH in tumors. When nigericin and hydralazin are associated there is a slight increase in intracellular acidification, but importantly the duration of the acidification is increased (69). The authors also found that the nigericin-HDZ association killed tumor cells by decreasing intracellular pH. HDZ alone did not lower intracellular pH, but decreased extracellular pH (70). When hyperthermia and HDZ were used simultaneously, extracellular pH decreased significantly (71).

2.9. Hydralazine decreases interstitial fluid pressure

Solid tumors usually have a significantly increased interstitial fluid pressure (72). This pressure decreases the access of chemotherapeutic drugs to the malignant cell (73), and also plays a role in promoting epithelial-mesenchymal transition (74), and other pro-tumoral effects (75). Hydralazine has been found to decrease interstitial fluid pressure in tumors without affecting normal tissues (76, 77).

2.10. Hydralazine facilitates nanoparticle penetration in desmoplastic tumors

Desmoplastic tumors such as pancreatic cancer adenocarcinoma and desmoplastic melanomas have a built in barrier for the penetration of drugs and nanoparticles. Using nanoparticles loaded with HDZ after three days of treatment the tumor stroma was significantly reduced and decreased the immunosuppressive environment. Furthermore, the HDZ liposomes increased the penetration of nanoparticles in the tumor (78).

2.11. DNA methyltransferases (DNMTs) inhibition

It is very frequent to find that malignant cells have extensive alterations of DNA methylation. Focal DNA hypermethylation at certain sites silences tumor suppressor genes. Inhibition of DNA methyltransferase impedes silencing these genes, and this is precisely the function of HDZ. Pharmacological inhibition of DNMTs is completed by the proteasomal degradation of these enzymes (79, 80).

There are many DNMT inhibitors, 5- azacytidine is the best known and most used, however they do not work in solid tumors and they induce a cytotoxic response (81). Evidence shows that HDZ does not have these limitations: it seems to work in solid tumors and general toxicity is very low.

2.12. Hydralazine in myelodysplasia

Myelodysplastic syndrome is a group of various hematopoietic stem cell disorders that are characterized by ineffective hematopoiesis and entail a high risk of progression towards acute myeloid leukemia (82). The association HDZ with valproate has shown some encouraging results in a disease for which there is no established and effective treatment (83).

Candelaria et al. (84) treated 14 patients on a compassionate basis. Five patients had a complete response, one a partial response, and two became transfusion independent, 3 progressed to acute myeloid leukemia. The median OS was not reached in the eight patients who saw clinical benefits.

2.13. Hydralazine inhibits glutamate oxaloacetate transaminase 1 (GOT1)

Wu et al. (24) found that HDZ was an effective inhibitor of GOT1. This enzyme is an important player in the altered cancer metabolism by regulating mechanisms to meet nutrient requirements (85). Inhibiting GOT1 increases cell dependency on glucose and can potentially induce growth arrest. Its over-expression is considered a marker of poor prognosis in acute myeloid leukemia (86).

2.14. Hydralazine toxicity

Although it has low toxicity, a lupus type syndrome was sometimes found when the drug was used for hypertension treatment (87). For a complete review on this issue see reference (88).

3. Discussion

Hydralazine is an old and well known drug with a good safety profile that has shown notable anti-cancer effects.

The main mechanism of its anti-neoplastic effects is the inhibition of DNA methyltransferases. This allows the re-expression of tumor suppressor genes that have been silenced by the tumor. Another interesting effect is HDZ`s ability

to inhibit glutamate oxaloacetate transaminase 1. Notably, there are many other effects important for tumor treatment, such as reduction of interstitial fluid pressure, increased penetration of nanoparticles into the tumor, and reduction of stroma in desmoplastic tumors.

The association of HDZ with valproate has shown synergic anti-tumoral effects. There is already a compound that has both drugs and has shown remarkable effects in the treatment of myelodysplasia and some solid tumors.

However, there are also some pro-tumoral effects, mainly increased hypoxia which may play against the drug repositioning.

Analyzing pro- and antitumoral actions, it seems that the latter significantly surpasses the first.

Neither HDZ nor valproate nor their association represent a stand-alone scheme, but they can be an efficient complementary treatment to be added to mainstream chemotherapy treatment, without adding major toxicity.

4. Conclusions

Hydralazine is an inhibitor of DNA methyltransferases thus impeding the inactivation of tumor suppressor genes which restores their activity. HDZ`s association with an inhibitor of histone deacetylase such as valproate has shown to be beneficial when used with classic chemotherapeutic drugs. However, HDZ is not a stand-alone drug but rather a complementary treatment.

The several ongoing clinical trials makes it possible to predict that it will be incorporated into chemotherapy schemes in the near future. Other than in Mexico, it has not been approved yet, for the treatment of myelodysplastic syndromes and metastatic, recurrent, or persistent cervical cancer in association with standard chemotherapy.

Hydralazine associated with valproate has a weak but clear anti-tumoral effect.

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