

Overview of Antabuse[®] (Disulfiram) in Radiation and Cancer Biology

Yaqi Jia
Tao Huang

Department of Hepatobiliary Surgery,
The Affiliated Cancer Hospital of
Zhengzhou University, Zhengzhou,
People's Republic of China

Abstract: Antabuse[®], generic name disulfiram, has been extensively used in daily clinical practice to treat alcohol abuse. In vivo and in vitro experiments have demonstrated that disulfiram was capable of inhibiting tumor cell proliferation; clinical studies have indicated that the administration of this drug was associated with favorable survival, whilst in vitro experiments have elucidated the anticancer mechanism of disulfiram. In addition, radiation and cancer biology studies have shown that disulfiram can protect normal cells and sensitize tumor cells during radiotherapy. This review aims at describing the antitumor activity of disulfiram in both preclinical studies and clinical trials, whilst focusing on the advances of this drug in radiation and cancer biology, and the promise of repurposing it as a novel sensitizer to, and protector against, radiation on the incoming clinical studies.

Keywords: disulfiram, cancer biology, radiotherapy, overview

Introduction

Cancer is a major public health problem. It is one of the leading causes of death across the world.¹ Factors such as ageing, infections, tobacco, diet, obesity, alcohol abuse, air pollution, diet, epigenetic and genetic alterations are all known to contribute to carcinogenesis in humans.^{2,3} Primary cancer may be treated with radical surgery, radiotherapy, systemic chemotherapy, targeted therapy, hormone replacement therapy and/or immunotherapy.⁴⁻⁶ There has been significant progress with all of these treatment options, but a high tumor-related morbidity and mortality still exists. Therefore, an acceleration in the development of anticancer drug is still required.

Developing new medicines is a costly and time-consuming process, with high failure rates. Because of this, investigators have shifted their focus to pre-existing drugs that may have secondary anticancer activity.⁷ Antabuse, generic name disulfiram (DSF), is one of these drugs. Disulfiram has been approved to treat alcoholism for more than sixty years, only recently has it emerged as a candidate for drug repurposing in anticancer therapy. Several investigators have described the antitumor efficacy of disulfiram both in vivo and in vitro. Disulfiram also appears to be well tolerated and cause minimal side effects.⁸⁻¹⁰

Recently, a Danish-Czech-US research group retrospectively analyzed the Danish nationwide demographic and health registries. More than 3000 patients diagnosed with cancer took disulfiram between 2000 and 2013. Compared with the patients who stopped taking the drug, the cancer mortality was 34% lower in those who stayed on disulfiram. Further investigation revealed that disulfiram chelates copper and converts into bis

Correspondence: Tao Huang
Department of Hepatobiliary Surgery,
The Affiliated Cancer Hospital of
Zhengzhou University, No. 127 Dongming
Road, Zhengzhou, 450008, Henan
Province, People's Republic of China
Tel/Fax +86-371-65587276
Email gandansanht@163.com

(diethyldithiocarbamate)-copper complex. The complex selectively targets NPL4-dependent segregase, a component of the ubiquitin proteasome system that is altered in tumor cells, thereby leading to increased cell death.¹¹ The cellular mechanisms of action for disulfiram on cancer cells have been well elucidated. During the past few decades, many studies have demonstrated that disulfiram is metabolized to diethyldithiocarbamate. Diethyldithiocarbamate has antioxidant effects on cells, thereby serving as protection against radiation in normal tissues. Not only did disulfiram protect normal cells from radiation, it also appeared to enhance the sensitivity of cancer cells towards radiation.^{12–16} This review discusses and elaborates the unique role of disulfiram in cancer radiotherapy (Figure 1).

Radioprotective Activity of Disulfiram

The radioprotective effects of disulfiram have been thoroughly investigated. Stromme et al described that disulfiram was metabolized to diethyldithiocarbamate (DTC) in mice, and that these animals were well protected against ionizing radiation.¹⁷ Other studies have shown that radiation exposure produces free radicals, which are highly reactive. Disulfiram is a potent antioxidant that protects deoxyribose against damage in normal cells.^{12,18} In the L-929 mouse fibroblast cell lines, disulfiram increased radiation sensitivity in tumor cells while reducing radiation toxicity in normal tissues. This observation was concentration dependent. Furthermore, disulfiram's radiation modifier effect was achieved through its major metabolite DTC.¹⁹ Although the molecular

mechanism of disulfiram in normal tissue remains largely unknown, these observations generated enthusiasm for the idea that disulfiram could protect against radiation.

One of the observations was made in response to gamma radiation. Following exposure to gamma radiation, radiation induced damage in normal cells lead to a decreased quantity of the supercoiled form of plasmid pBR322 DNA (deoxyribonucleic acid). Despite being irradiated at a dose of 300Gy, the plasmid DNA assumed complete protection in the presence of disulfiram; when the radiation dose was increased to 600 Gy, a near-linear increase of the membrane lipids peroxidation was detected and the administration of disulfiram was capable of reducing the damage. In mice models, whole body irradiation was delivered after the administration of disulfiram. Cellular DNA damage and membrane lipids peroxidation reduced in the liver of mice treated with disulfiram.¹²

Based on these studies, it appears that disulfiram protects DNA from radiation induced damage in normal tissues and warrants further investigation as a radioprotector.

Disulfiram Enhances Radiation Sensitivity of Tumor Cells

In the past few decades, much progress has been made in radiotherapy. However, there is still a high demand for improved therapies as local-regional recurrence rates remain significant.^{20,21} The main problem is that it is difficult to deliver a high dose of radiation to a tumor whilst limiting the dose to normal surrounding tissues. To get around this problem, radiobiologists have tried to

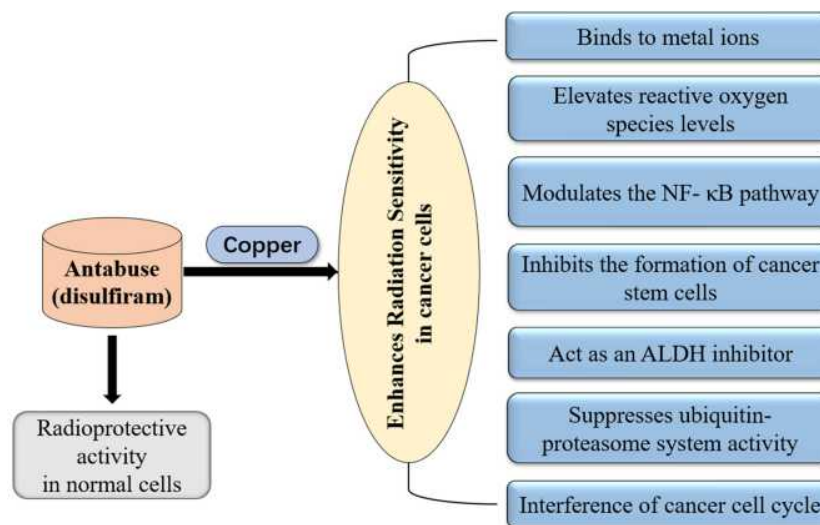


Figure 1 Mechanisms of disulfiram in radiation protection and disulfiram-copper complex enhance the efficacy of radiotherapy in tumor cells.

find ideal radiation sensitizers to improve local tumor control rates.

Disulfiram is capable of enhancing the radiation sensitivity of cancer cells in a variety of ways.^{12–16} And one of the unique ways is through forming a complex with metal ions. A lack of metal ions decreases disulfiram's antitumor activity.²² Meanwhile, in human cancer patients, an elevated copper level has been detected in both the tumor tissues and the serum. Further investigations showed that copper is involved in the biological process of tumorigenesis and metastasis.^{11,23} This makes disulfiram an ideal antitumor drug. In a previous study, disulfiram's anticancer effect was shown to be copper-dependent. Disulfiram-copper complex inhibited breast cancer cell proliferation, but not in normal cells.²⁴ In addition, a synergistic interaction was found between copper-complexed disulfiram and radiotherapy; in human SK-N-BE neuroblastoma and UVW/noradrenaline transporter glioma cells, the efficacy of both external beam radiotherapy and targeted radionuclide therapy were enhanced by disulfiram in a copper-dependent manner. High concentrations of disulfiram induced oxidative stress, which was associated with tumor cell death; however, disulfiram's anticancer activity in low concentrations was copper-dependent.¹³ In addition, novel copper-based nanoparticle has been developed, this compound could be significantly activated by radiotherapy and was efficient in inhibiting human breast cancer cells (MCF-7) proliferation.²⁵ Disulfiram combined with copper-based nanoparticles were demonstrated to enhance the efficacy of radiotherapy in esophageal cancer.²⁶ Although there is little evidence, to date, in clinical applications, this unique property makes disulfiram essential to radiation oncology.

Disulfiram Causes Reactive Oxygen Species (ROS) Levels Alteration

Superoxide radicals play a crucial role in radiation-induced cell death, whereas cancer cells contain a low level of superoxide dismutase.^{27,28} Disulfiram and one of its metabolites DTC have been demonstrated to increase oxidative stress in tumor cells.²⁹ Consequently, there are some studies focusing on the dynamic change in intracellular ROS levels in response to combined radiotherapy and disulfiram treatment. In Chinese hamster cell models, DTC, a copper chelating agent, was administered during the course of radiotherapy. Final results suggested that DTC inhibited the enzyme superoxide dismutase,

promoting superoxide radical mediated toxicity. Eventually, the tumor cell radiation sensitivity was enhanced.³⁰ In inflammatory breast cancer cellular models, a redox adaptive response means the cancer cells evade ROS-mediated death. The disulfiram and copper complex have emerged as a redox modulator that enhances radiation sensitivity by inducing oxidative stress mediated apoptosis in tumor cells. Importantly, no significant in vitro toxicity was observed in normal cells.²² The combination of disulfiram and copper enhanced both radiation sensitivity and chemotherapy sensitivity via upregulating ROS levels in head and neck squamous cell carcinoma.³¹ Park et al treated head and neck squamous cell carcinoma with disulfiram and copper complex, an increased ROS formation was observed and the complex significantly induced autophagic cell death.³² In glioblastoma, disulfiram acted as a novel ferroptosis inducer which was effective in triggering lysosomal membrane permeabilization and producing ROS, and finally improved the efficacy of radiotherapy.³³ Disulfiram is capable of regulating intracellular antioxidative defense systems, but is harmless to normal tissues; thereby, serving as a novel and promising radiosensitizing agent for the treatment of cancer.

Disulfiram Targets Cancer Stem Cells (CSCs)

Previous studies have indicated that CSCs contribute to the inherent resistance of tumor cells to radiotherapy.³⁴ Targeting CSCs is, therefore, a promising approach to kill off a tumor's regenerative capacity following radiotherapy. In vivo and in vitro studies of pancreatic ductal adenocarcinoma implied that standard chemoradiation regimes accelerated the generation of CSCs, defined as Aldehyde dehydrogenase (ALDH) overexpressing tumor cells.¹⁴ ALDH belongs to an enzyme super family that catalyzes the oxidation aldehydes.³⁵ Over the past few decades, several studies have shown that ALDH1 is a marker of CSCs and tumor initiating cells.^{36,37} As a result, ALDH could be an important target in anticancer therapy. Disulfiram treats alcoholism through its ability to inhibit the enzymatic activity of ALDH.³⁸ Recent studies have suggested that disulfiram combined with radiotherapy are efficacious at suppressing CSCs. Choi et al reported that disulfiram can penetrate the blood brain barrier and accumulate in the brain. The accumulation of disulfiram in the brain induces apoptosis and, by inhibiting ALDH, decreases proliferation of the brain tumor initiating cells.³⁹

The NF- κ B Pathway

Several studies have demonstrated a role for NF- κ B signaling in CSC biology. The administration of disulfiram-copper complexes in combination with irradiation, *in vitro*, inhibited CSCs via the NF- κ B stemness gene pathway. The same study also used a breast cancer xenograft mouse model to show that tumor growth and metastasis were inhibited and apoptosis was induced by disulfiram, when combined with radiotherapy.⁴⁰ Disulfiram-copper complex combined with chemoradiotherapy was found to be effective in inhibiting CSCs and tumor cells via downregulation of the NF- κ B pathway; with an efficacy of 42% compared with 30% for the standard chemoradiotherapy regime.¹⁴

Disulfiram Act as an ALDH Inhibitor

Other cellular mechanisms of disulfiram in combination with radiotherapy, in CSCs, have been observed. CSCs of atypical teratoid/rhabdoid tumor express ALDH. Disulfiram, as an irreversible ALDH blocker, induces apoptosis in irradiated tumor cells, whilst increasing cell cycle arrest and autophagy by reducing DNA double strand break repair. In atypical teratoid/rhabdoid tumor mouse model, disulfiram combined with radiotherapy inhibited tumor growth and produced a survival benefit.¹⁵ Several mechanisms by which disulfiram targets CSCs have been shown. This gives further support to the idea that disulfiram may be an important radiation sensitizer in antitumor therapy, particularly in brain cancers.

The Inhibition of Ubiquitin-Proteasome System (UPS)

The UPS is involved in many biological processes, including cellular protein catabolism, signal transduction, cell cycle progression, apoptosis, chromosome maintenance.⁴¹ In recent years, several studies have indicated that UPS participates in the modulation of radiation induced responses in cancer.^{42,43} As previously mentioned, disulfiram is known to alter the intrinsic radiation sensitivity of cancer cells. In human radiation resistant cell lines, disulfiram combined with copper was an effective proteasome blocker, suppressing the activation of the NF- κ B pathway and enhancing the effect of radiation treatments on killing cancer cells.⁴⁰ Disulfiram-copper complex impaired DNA repair pathways in a glioblastoma cell line by inhibiting proteasome activity and acting as a radiation sensitizing

agent.⁴⁴ Previous studies described radiation induced protein burden in tumor cells.^{45,46} Disulfiram-copper was able to inhibit proteasome activity and misfolded protein accumulation in the tumor cells. The complexes have been shown to act, via its effect on proteasome function, as a radiosensitizer both *in vitro* and *in vivo*. Therefore, the combined strategy increased the protein burden and results in cell apoptosis.

The Interference of Cancer Cell Cycle

The radiation sensitivity of cancer cells varies in different phases of the cell cycle. Tesson et al reported that disulfiram, in the presence of copper supplement, could be considered as a cell cycle specific cellular radiation sensitizer. The disulfiram-copper complex works by inhibiting the proteasome activity. Only 0.3 μ M of this complex was required to achieve the maximum anticancer effect of radiotherapy on the neuroblastoma cell line SK-N-BE and the glioma cell line UVW.¹⁶ Hassani et al demonstrated disulfiram copper complex caused the disturbance of the ROS balance and induced G0/G1 cell cycle arrest in acute myeloid leukaemia cell lines.⁴⁷ These results, together, justify the evaluation of disulfiram as an adjuvant agent in patients receiving radiotherapy.

Future Perspective

The evidence of disulfiram's radiation sensitizing activity and antitumor effects is accumulating. Laboratory studies have also revealed that disulfiram has an anti-angiogenic effect and causes epigenetic modifications.^{48,49} However, investigations in the context of radiation biology are extremely rare. There is still some disagreement over the conclusions of some of the *in vitro* and *in vivo* studies and the underlying mechanism of disulfiram's radiosensitization effect remains to be fully elucidated. There are nine ongoing clinical trials focusing on the application of disulfiram as an anticancer agent worldwide. Only one of these clinical trials is studying the disulfiram-copper complex combined with radiotherapy (Table 1).

The lack of large-scale, prospective, observational studies is limiting the application of disulfiram as a radiosensitizer and radioprotector in clinical practice. Despite this, our knowledge of disulfiram and its molecular mechanisms, by which it regulates normal cells and

Table I Ongoing Cancer Clinical Trials Using DSF in the Treatment of Cancer

NCT Number	Year	Center	Tumor Type	Phase	Interventions	Recruitment
NCT0190716	2013	Washington University School of Medicine, United States;	•Glioblastoma	Early Phase I	Temozolomide + DSF/Copper gluconate	Active, not recruiting
NCT02715609	2016	•Washington University School of Medicine, United States; •University of Calgary, Canada;	•Glioblastoma Multiforme	•Phase I •Phase II	Surgery + Radiation + Temozolomide + DSF/Copper Gluconate	Recruiting
NCT0332334	2017	•University Hospital Olomouc, •The Institute of Molecular and Translational Medicine, Czech Republic;	•Breast Neoplasm Female •Metastatic Breast Cancer	Phase II	DSF	Recruiting
NCT0267897	2017	•St.Olavs University Hospital, Norway; •Sahlgrenska University Hospital, •Ryhov County Hospital, Sweden •Linköping University Hospital, •Lund University Hospital, •Karolinska University Hospital, •Uppsala University Hospital, •Örebro University Hospital, Sweden;	•Recurrent Glioma •Recurrent Glioblastoma	•Phase II •Phase III	DSF/Copper + Alkylating Agents	Recruiting
NCT02963051	2017	Duke University Medical Center, United States;	Prostate Cancer	Phase I	DSF/Copper gluconate	Recruiting
NCT0177791	2017	•Olympion Medical Center, •University of Ioannina, Greece; •University of Eastern Finland; •University of Ulm, German;	Glioblastoma Multiforme	Phase II	Temozolomide and DSF/ Copper	Not yet recruiting
NCT0303413	2017	•Beaumont Hospital, •Washington University School of Medicine, •John Theurer Cancer Center, •Lenox Hill Hospital, •University of Cincinnati, •Vanderbilt Ingram Cancer Center, •Baylor University Medical Center, •Huntsman Cancer Institute, United States;	Recurrent Glioblastoma	Phase II	DSF/Copper	Recruiting
NCT0315177	2017	Sahlgrenska University Hospital, Sweden;	Glioblastoma	Phase I	DSF versus Metformin	Not yet recruiting
NCT0336365	2018	Aurora St. Luke's Medical Center, United States;	Glioblastoma/ Glioblastoma Multiforme	Phase II	DSF/Copper gluconate + Temozolomide	Not yet recruiting

cancerous cell response to ion irradiation, has continued to grow. This provides an excellent opportunity to develop a therapy that may decrease the local failure rates and toxicity of radiotherapy.

Conclusion

Finding a new use for an approved drug is appealing. Disulfiram is an old, inexpensive and tolerable drug to treat alcohol abuse, which has now been shown to

sensitize cancer cells to radiotherapy. The studies reviewed here show that the anticancer activity of disulfiram, along with its copper dependence, has been well elucidated. While the radioprotective effects of disulfiram in normal cells and radiosensitizing activity in tumor cells still require a full investigation, the utility of this drug as a potential radiosensitizer is well recognized. One benefit of disulfiram being an approved drug, is that it has already passed safety testing. This, together with the results of the studies reviewed here, reaffirm the need for a clinical evaluation of disulfiram as a pre-existing drug that may increase the efficacy and safety of radiotherapy.

Abbreviations

ALDH, aldehyde dehydrogenase; Cu, copper; CSC, cancer stem cells; DSF, disulfiram; DTC, diethyldithiocarbamate; DNA, deoxyribonucleic acid; NF- κ B, nuclear factor kappa B; NPL4, Nuclear protein localization protein 4 homolog; ROS, reactive oxygen species; UPS, ubiquitin-proteasome system.

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Disclosure

The authors declare that they have no competing interests.

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