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Potential use of edaravone to reduce specific side effects of chemo-, radio- and immuno-therapy of cancers

Christian Bailly

OncoWitan, Lille (Wasquehal) 59290, France

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ABSTRACT

The drug edaravone (EDA) is prescribed for the treatment of patients with amyotrophic lateral sclerosis or after an acute cerebral infarction. This synthetic pyrazolone derivative is a potent scavenger of oxygen free radicals and also functions as a modulator of transcription factors, repressing NFκB and activating Nrf2, to regulate oxidative stress. EDA displays complementary anti-oxidative and anti-inflammatory effects. The injectable small molecule is currently investigated for the treatment of several non-neurological diseases. The potential interest of EDA in oncology is reviewed here. EDA is a mild antiproliferative agent but has been found to enhance significantly the anticancer and antimetastatic activities of irinotecan in a colon cancer model. Anticancer derivatives of EDA have been designed but they generally display a limited antiproliferative activity. The antioxidant and anti-inflammatory activity of EDA can be best exploited to protect non-tumor cells from damages induced by chemotherapeutic drugs and radiations. Notably EDA can reduce the renal dysfunction induced by cisplatin, the neurotoxicity of cyclophosphamide and the cardiotoxicity of doxorubicin. Upon treatment with EDA, a significant improvement in neurologic symptoms has been observed in patients with nasopharyngeal carcinoma after radiotherapy. The drug could be used to limit radiation-induced brain injury or oral mucositis. EDA was found to ameliorate autoimmune thyroiditis (Hashimoto thyroiditis), which is a frequent side effect observed after treatment of cancer patients with monoclonal antibodies targeting the immune checkpoint PD-1. Therefore, EDA could also be useful to reduce specific side effects of immuno-therapy. Collectively, the information suggests that the medical use of EDA, a drug with a proven safety after 18 years of use in brain-related Human diseases, could be extended to cancer-related conditions.

1. Introduction

Edaravone (EDA) is a potent antioxidant used since 2001 in Japan for the management of cerebral infarction (stroke). Later the drug was approved worldwide for the treatment of adult patients with amyotrophic lateral sclerosis (ALS, also called Lou Gehrig's disease), a progressive neurodegenerative disorder of motor neurons accompanied with muscle atrophy. It was initially approved in Japan and South Korea in 2015 and then in different countries; it has received approval from US-FDA in May 2017 and Chinese-NMPA in August 2019 for the treatment of ALS [1,2]. Chemically, EDA is a phenyl-pyrazolone derivative showing a high reactivity with oxidative free radicals, through electron transfer from edaravone anion (Fig. 1). Administered iv – there is no oral dosage formulation of EDA - the drug can easily cross the blood-brain barrier (BBB) and is weakly subjected to efflux by the P-gp. EDA displays a high brain penetration capacity and lipophilic formulation of EDA can further enhance the uptake into the brain [3]. EDA mainly reacts with oxygen radicals by oxidation into 4-oxoedaravone and then OPB (2-oxo-3-(phenylhydrazono)butanoic acid), the peroxidation product. It reacts also with peroxynitrite as well as lipid peroxyl radicals. EDA exhibits a keto-enol tautomerism, with three isomeric structures: the keto, enol and amine forms and the anion form also possesses three resonance structures (Fig. 1) [4]. The potent radical-scavenging and antioxidant activities of EDA account for its clinical efficacy. The drug is primarily used as a neurovascular protective agent for the management of cerebral infarction and ALS but other clinical indications have been discussed such as the management of glaucoma to lower intraocular pressure [5] or to limit the progression of cardiac dysfunction in heart failure [6,7]. In fact, the use of the drug to treat various non-neurological diseases and conditions has been proposed: to treat retinal, myocardial, lung, intestinal, liver, pancreatic, renal, bladder and testicular injuries, but also sepsis and burns [8].

Abbreviations: ALS, amyotrophic lateral sclerosis; BBB, blood-brain barrier; EDA, edaravone; IL, interleukin; NSC, neural stem cells; ROS, reactive oxygen species

E-mail address: christian.bailly@oncowitan.com, http://www.oncowitan.com.
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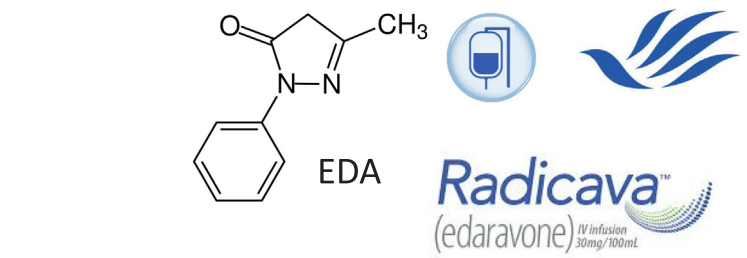
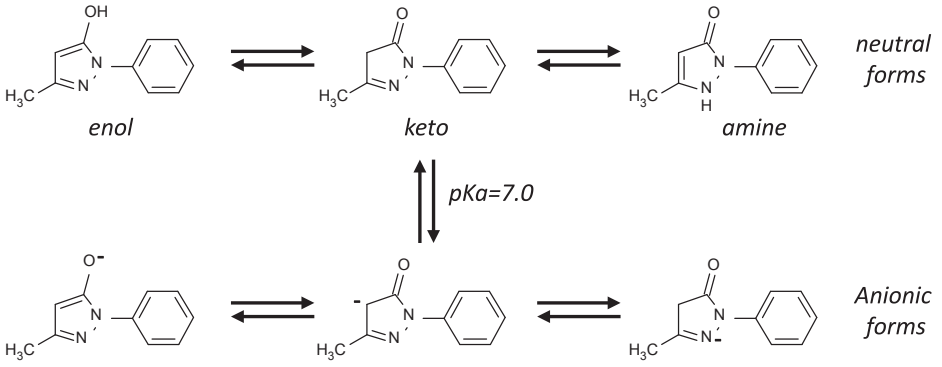


Fig. 1. Structure of Edaravone (3-methyl-1-phenyl-2-pyrazolin-5-one, formerly MC-186). The drug is sold under different brand names including Radicut® and Radicava® (Mitsubishi Tanabe Pharma Corporation, Japan), Nuravon™ (Abbott), Univone and Arone and others. The keto-enol tautomerism and resonance of EDA as well as the equilibrium between the neutral and anionic forms of EDA are represented.
Adapted from [4].



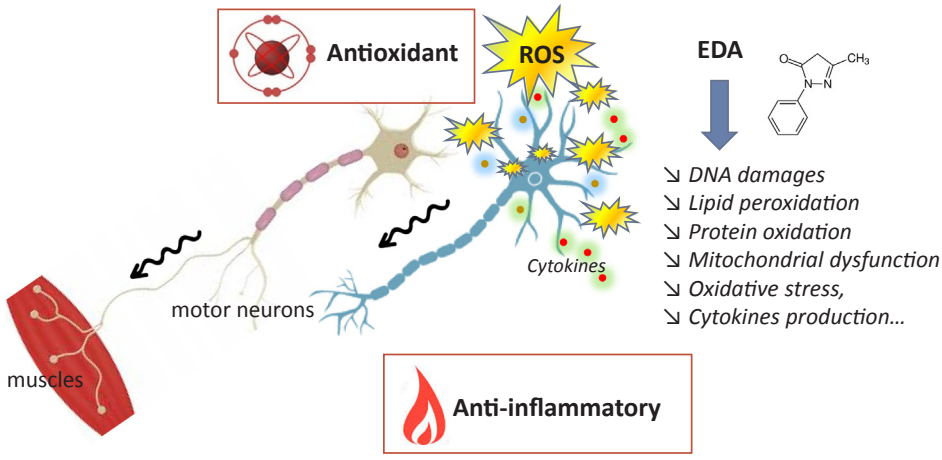


Fig. 2. Illustration of the mechanism of action of EDA which provides a cerebral neuroprotection by reducing oxidative stress and inflammation. The scavenging of reactive oxygen species (ROS) by EDA reduces the extent of DNA damages, oxidation of lipids and proteins, thus diminishing the cellular oxidative stress. The drug induces a reduction of the production of cytokines (such as IL-6, IL-10, IL-18, TNF-α, IL-1β) leading to the anti-inflammatory response. These effects limit the neuronal dysfunctions.

In addition to scavenging free radicals, EDA targets different intracellular signaling pathways suppressing the release of proinflammatory cytokines and the activation of inflammatory cells. In fact, EDA displays both anti-oxidative and anti-inflammatory effects (Fig. 2). Recently, novel key elements to clarify the mechanism of action of EDA have been published. The drug prevents the transfer of the transcription factor protein NFκB from the cytoplasm to the nucleus, whilst promoting the expression of the transcription factor Nrf2 (nuclear factor erythroid 2-related factor) known to regulate the expression of antioxidant genes (Fig. 3). The suppression of NFκB-mediated inflammatory activation and promotion of Nrf2 antioxidant pathway are two key processes that mediate EDA activities [9]. In recent years, NRF2 signaling has emerged as the central pathway that protects cells from variety of stressors; it plays a major role in inflammation [10]. The expression of NRF2 downstream genes maintain the oxidative homeostasis and cell survival. EDA was found to activate the Nrf2/ARE signaling pathway under different conditions, and this effect apparently underlies its protective effects against the oxidative damage associated with the disease considered, stroke, or Alzheimer's or other oxidative stress-associated pathologies [11–13]. The capacity of EDA to reduce systemic inflammatory responses under oxidative stress is important to underline. EDA treatment was found to decrease a range of pro-inflammatory cytokines/chemokines (such as IL-1β, IL-6, IL-10, TNF-α) in various pharmacological models and in Human [14–16]. Thus, EDA has multiple biological effects acting as an oxygen radical scavenger, a modulator of NFκB and Nrf2 activities, and an inhibitor of chemokines production, limiting the development and progression of inflammatory cascades which are implicated in various disease processes. Because these oxidative and inflammatory processes are implicated in cancer as well, I have examined the potential interest of EDA in cancer therapy, either as a direct anticancer agent alone or in combination, or as an indirect support to alleviate the adverse side effects of various anticancer treatments. As discussed here, EDA presents little interest as an anticancer agent *per se* but could be much more useful as a protector, to reduce the side effects of cancer radio-, chemo- and immuno-therapies.

2. Limited anticancer activities of edaravone and derivatives

EDA alone displays modest antiproliferative effects against tumor cells. The drug was found to dose-dependently limit tumor growth of some cancer cell lines *in vitro* (e.g. MCF-7 breast cancer cells) but the effect was very limited, essentially observed at high concentrations

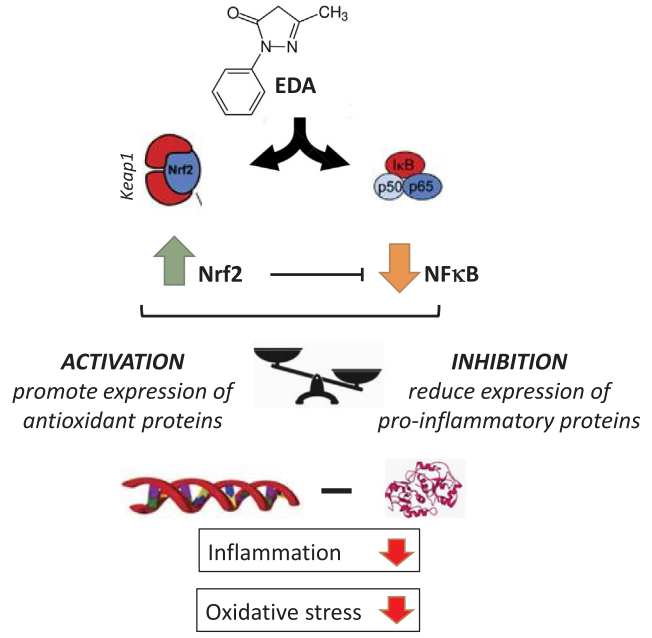


Fig. 3. EDA improves the antioxidant defense via an upregulation of Nrf2 expression and inhibition of the pro-inflammatory factor NFκB. EDA modulates the crosstalk between the two transcription factors. EDA-induced Nrf2 activation (via Keap1…) promotes the expression of antioxidant proteins, while NFκB inhibition (via p50/p65…) reduces the expression of pro-inflammatory proteins. Nrf2 antagonizes NFκB activation through proteasomal activation. The complementary action on the Nrf2/NFκB pathway leads to a reduction of oxidative stress and inflammation by EDA.

(100–300 μM) and without effect on cell viability [17]. By itself, EDA is a weak cytotoxic agent but it can react with another compound to generate a more potent cytotoxic product. A case was described with a pterin derivative, DFP that is used to produce singlet oxygen ($^1O_2$) under UV-A radiation, for anti-cancer photodynamic therapy. EDA was found to form a cell-permeable, cytotoxic ROS-generating adduct DFP-E [18,19].

Certain anticancer drugs have the capacity to activate the transcription factor NFκB which is one mechanism of tumor resistance and survival. This is the case of irinotecan (CPT-11), a conventional cytotoxic drug targeting topoisomerase I, largely used to treat solid tumors, in particular colon cancers [20]. The blockade of NFκB activation can shift the death/survival balance toward apoptosis. EDA has been shown to inhibit activation of NFκB-induced by SN38, the active metabolite of CPT-11 and thereby to enhance apoptosis and its antitumor effects both *in vitro* and *in vivo*. The combination of EDA and CPT-11 reduced colon26 tumor growth in mice and decreased the number of pulmonary metastases, much more effectively than CPT-11 alone [21]. The capacity of EDA to inhibit activation of NFκB and to suppress oxidative stress and endoplasmic reticulum stress (EDA is known to decrease the induction of the stress marker GRP78) should also confer to EDA a capacity to protect against CPT–11–induced intestinal mucosa injury. As such, EDA could improve the anticancer activity and decrease the intestinal side effects of CPT-11.

Numerous anticancer pyrazole derivatives have been designed and synthesized over the past ten years but there are not many pyrazolone derivatives of EDA. A few innovative compounds are indicated in Fig. 4. Recently, the phenyl-pyrazolone derivative DPDHN was found to reduce tumor cell proliferation, with a modest efficacy [22]. In another series of pyrazolones, compound 9 proved to be active *in vitro* and *in vivo* at reducing tumor growth in a dose-dependent manner. Notably, this compound inhibited the subcutaneous growth of multidrug resistant KBv200 cells in mice. It required complexation with Cu to exert its antiproliferative activity [23]. Another interesting compound is the pyrazolone derivative TELIN which inhibits human telomerase. This compound binds to the telomerase enzyme, not to the quadruplex DNA target, to function as an enzyme blocker [24]. But no cellular information was reported with this compound. In fact, only two studies refer directly to the design and synthesis of antitumor EDA analogues. The first, in 2011, described the synthesis and structure–activity relationships for a series of 4-aminomethylidene derivatives of EDA and compound 3q was found to elicit a noticeable antiproliferative activity against certain cancer cells [25]. For example, this compound proved to be about 10-times more potent that EDA against the breast cancer cell line MDA-MB-453, with an IC_{50} of about 10 μM (which is still low compared to conventional cytotoxic drugs) [25]. More recently, another series of anticancer EDA analogues was designed and a few compounds showed a superior antiproliferative activity against cancer cells compared to EDA. One of the best compounds in this series, compound 7c, showed a modest cytotoxic activity *in vitro* [26].

In the next sections, the potential use of EDA as a cytoprotector against toxicities caused by some chemo-, radio- and immuno-therapeutic drugs is discussed (Fig. 5).

3. Potent protection from chemotherapy-induced toxic effects

The cell-protective activity of EDA has been exploited to limit the side effects of certain anticancer drugs. Notably cisplatin, one of the most widely used cytotoxic agents for various solid tumors, induces frequent dose-dependent toxic side effects, in particular oto-, nephro-, gastrointestinal- and neuro-toxicities. These secondary effects reduce the life quality of patients and may require dosage adjustments weakening the treatment effect. EDA was tested as an antioxidant to alleviate cisplatin-induced neurobehavioral deficits in rats. An *in vivo* treatment with EDA was found to up-regulate Nrf2/HO-1 gene expression and to prevent cisplatin-induced NFκB activation. These biochemical changes led to a reduction of the neurobehavioral and cognitive deficits observed in rats treated with cisplatin [27]. Two studies reported that EDA can protect against cisplatin-induced ototoxicity by preventing apoptosis and limiting ROS production in cells and in a zebrafish model [28,29]. Other studies have shown that EDA may be potentially useful to prevent acute renal failure induced by cisplatin. The treatment with EDA attenuated the renal dysfunction and renal tubular damages in rats cotreated with cisplatin (i.p.) and EDA (i.v.) [30–32]. EDA limits drug-induced DNA damages in renal proximal tubules. Moreover, a recent study showed that EDA ameliorated also cisplatin-induced renal injury in the chronic phase in rats, with a reduction of proximal tubule injury, interstitial fibrosis and mononuclear cell infiltration [33]. Collectively, these studies provide a rational to investigate further the protective effects of EDA in cancer patients treated with cisplatin.

Very recently, the use of EDA to overcome the neurotoxicity of the anticancer drug cyclophosphamide was proposed. High-dose cyclophosphamide - used to treat metastatic breast cancer, certain lymphoma or leukemia - can lead to severe nephrotoxicity and neurotoxicity. In rats, the co-administration of EDA was found to ameliorate the behavioral and histopathological changes induced by cyclophosphamide [34].

The cardiotoxicity of anthracycline cytotoxic drugs is a major issue, frequently limiting the efficacy of the cancer treatment. Patients receiving doxorubicin or daunorubicin are at risk of cardiomyopathy and cardio-protection measures are often needed. EDA was found to prevent doxorubicin-induced cardiac deterioration *in vivo* and apparently does not affect daunorubicin's anticancer effect [35]. Interestingly in a toxicity study performed in dogs, EDA was found to alleviate the cardiac abnormalities produced by doxorubicin. Pretreatment with EDA improved the biochemical, electrocardiographic and physiological parameters characteristic of the anticancer drug-induced cardiac injury [36].

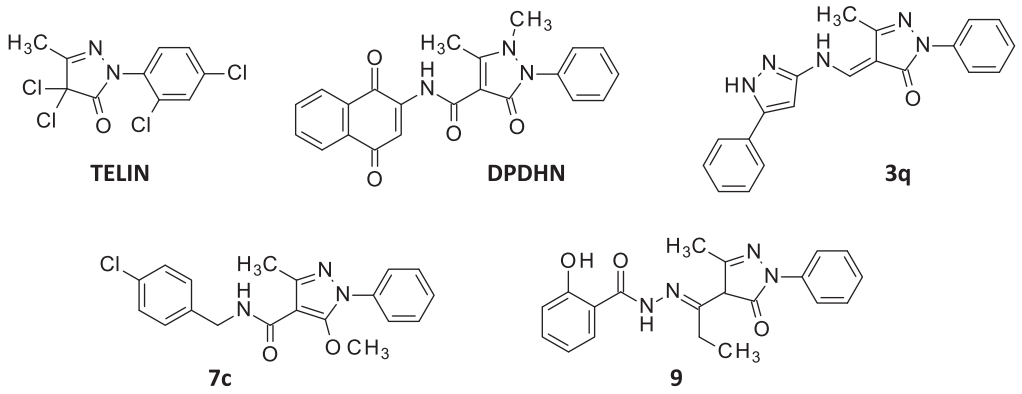


Fig. 4. Chemical structures of selected pyrazolone derivatives structurally related to EDA which have shown antiproliferative activities: DPDHN [22], TELIN [24], compounds 3q [25], 7c [26] and 9 [23].

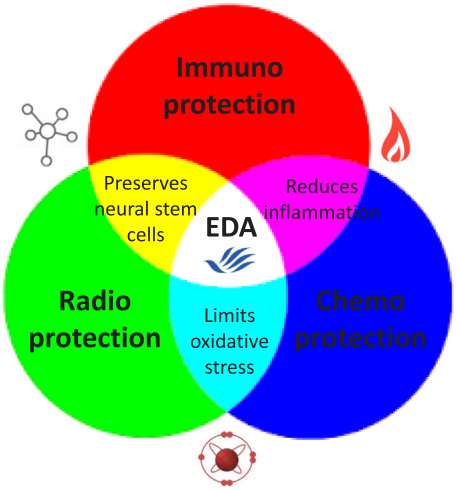


Fig. 5. EDA and cancer therapy. The drug can protect non-tumor cells from the oxidative damages and inflammation induced by chemo and radiotherapy of cancer. It could also help to alleviate the unwanted effects of immuno-therapy, such as autoimmune thyroiditis induced by anti-PD-1 antibodies, via its anti-inflammatory action.

4. Management of radiotherapy-induced side effects

EDA displays significant radioprotective effects. It can protect neurons of the hippocampus from cell death after irradiation [37]. *In vitro* at high concentrations (3 mg/ml), the drug was found to suppress apoptosis induced by X-ray in human T-cell leukemia MOLT4 cells, by inhibiting p53 and caspases [38]. EDA significantly inhibits γH2AX foci formation in MOLT-4 cells after irradiation [39] and reduces DNA damage in γ-irradiated lymphocytes [40]. But at low concentrations (0.75 mg/ml), EDA enhanced X-ray-induced apoptosis of cell lines harboring p53 wild-type status, such as MOLT-4, Nalm-6, and HepG2 [41]. The radioprotection effect has been observed also *in vivo* after ip administration of EDA to mice, the drug increased the lethal dose of radiation [42]. Interestingly, EDA can protect neural stem cells (NSC), but not brain tumor cells, from cell death after irradiation. It was found to restore the differentiation and self-renewal ability of NSC after irradiation, whereas the less sensitive brain tumor cells were not affected [43]. Thus, EDA could be useful to preserve neurogenesis after radiation therapy and to limit radiation-induced brain injury. In a population of 154 patients with nasopharyngeal carcinoma, a noticeable improvement in neurologic symptoms was observed in the majority (61%) of patients treated with EDA [44]. This first clinical study suggested that EDA may be useful to reduce radiation-induced brain necrosis but, as pointed out recently, further evidence is needed to support the utility of EDA for the treatment of radionecrosis [45].

Radiation therapy can induce also major toxicities, in particular oral mucositis which is frequent in patients treated with radiotherapy for a head and neck cancer. Here again, the antioxidant effects of EDA can be useful to limit tissue damages. The oral mucositis score was reduced in a murine model of mucositis induced on the tongue tips of mice receiving a single high dose of X-rays in the presence of EDA versus no treatment [46]. Moreover, cancer chemo- and radio-therapy can cause salivary gland atrophy, resulting in low salivary secretion in cancer patients, which can potentially exacerbate oral ulcerative mucositis. EDA has been shown to suppress parotid acinar cells dysfunctions in primary culture, suggesting a benefic role in the prevention of salivary gland dysfunction [47].

5. Edaravone and immuno-therapy of cancer

Another remarkable pharmacological property of EDA can be underlined here: its recently demonstrated capacity to ameliorate autoimmune thyroiditis. EDA was found to dose-dependently mitigate thyroiditis severity in an experimental rat model through the involvement of ROS and HO-1 dependent STAT3/PI3K/Akt pathway [48]. In this study, EDA significantly increased mRNA levels of IL-10, IL-4, TNF-α and IFN-β, while inhibiting mRNA level of IL-17. This discovery opens interesting clinical perspective because autoimmune thyroid diseases (such as Graves' disease and Hashimoto thyroiditis) can arise after PD-1/PD-L1 blocking therapies in cancer patients. Therapy with immune checkpoint inhibitors, and in particular anti-PD-1-antibodies (e.g. pembrolizumab and nivolumab), are frequently associated with (sometime irreversible) thyroid dysfunctions including thyroiditis [49,50]. Hashimoto thyroiditis is associated with IL-17A secretion, leading to T cell activation [51]. Chronic inflammation surrounding tumor upregulates PD-L1 expression on tumor cells by the release of cytokines, which act to inhibit tumor destruction [52]. Therefore, it would be particularly interesting to investigate the potential effect of EDA to limit the incidence of autoimmune thyroiditis upon anti-PD-1 therapy. Based on the experimental data [48], one can anticipate that in cancer patients receiving a PD-1-targeted immune checkpoint inhibitor, EDA can decrease the incidence of autoimmune thyroiditis by decreasing the number of IL-17-positive T cells.

6. Discussion

EDA was developed first for the treatment of acute brain infarction and, a few years later, for the treatment of ALS. Today, the drug is currently investigated in a number of neurologic and non-neurologic pathologies [8]. As discussed here, EDA may be useful to improve specific cancer treatments. There are common genetic and metabolic characteristics between ALS and cancer (oxidative unbalance,

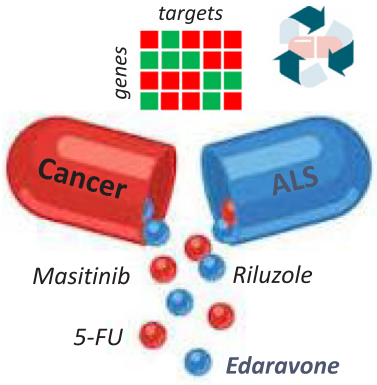


Fig. 6. Illustration of the interconnexion between cancer and ALS, with common genetic drivers or targets implicated in the pathologies (the small green and red squares illustrate common or distinct genes and targets). The two drugs approved for the treatment of ALS could be useful to improve cancer treatment (riluzole) or to limit the side effects of cancer therapies (edaravone). Conversely, the anticancer drugs 5-fluorouracil (5-FU, antimetabolite) and masitinib (kinases inhibitor) have shown activities in experimental models of ALS. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

inflammation processes). Epidemiological studies have suggested that ALS relates to cancer [53–55]. For example, the human mouse mammary tumor virus like-2 (HML-2) is activated in several tumors and has been related to prostate cancer progression and motor neuron diseases, including ALS [56]. Therefore, common therapeutic strategies may be developed (Fig. 6). Riluzole, the only other drug approved for the treatment of ALS, is also largely studied for its anticancer effects, notably for the treatment of brain tumors, prostate cancer and melanoma with a phase 2 trial ongoing [57–59]. Riluzole can block proliferation and/or sensitize cancer cells to radiation [60,61]. The drug functions as a glutamate release inhibitor (GRM1 antagonist), but its anticancer activity is apparently independent of GRM1 [62]. In parallel, a clinical trial is assessing the benefit of riluzole in the prevention of oxaliplatin-induced peripheral neuropathy [63]. At the same time, it is interesting to note that an inverse repurposing strategy, from cancer to ALS, is conducted with the tyrosine kinase masitinib (approved for mast cell tumors in dogs) to control neuroinflammation in ALS [64,65]. Certain anticancer microtubule stabilizing drugs (e.g., paclitaxel) can be repositioned for brain disorders including ALS [66,67]. Recently, the well-established antimetabolite 5-fluorouracil, used to treat many types of cancers, was found to be active in a mice model of ALS [68]. The natural products berberine and celastrol have shown activities in experimental models of both cancer and ALS [69–71]. The anti-inflammatory drug methylprednisolone also shows effects in both cancer and ALS [72]. The antileukemic drug imatinib has been considered for the treatment of ALS [73]. There are common epidemiological, genetic, and histopathological links between cancer and ALS [55]. The repositioning of an anti-ALS drug like EDA in oncology, and *vice-versa*, is really conceivable (Fig. 6).

A parallel can be established also with the mechanism of action of the triterpenoid drug omaveloxolone (RTA 408) which potently activates Nrf2 with subsequent antioxidant functions. This semisynthetic compound activates Nrf2, reduces NFκB phosphorylation and nuclear translocation, attenuates (ozone-induced) ROS release, decreases pro-inflammatory cytokine production and reduces the percentage of IL-17^+ γδT cells [74,75]. It is currently assessed in Human both for its antitumor activity and the management of brain diseases [76,77]. The two drugs EDA and omaveloxolone are structurally totally distinct but they share a similar mechanism of action that supports their potential interest both in cancer and brain diseases.

EDA is a low-molecular weight free radical scavenger that targets oxidative stress, a process largely implicated in neuronal and vascular damages. By potently scavenging free radicals, EDA can reduce the progression of diseases associated with an oxidative burst, such as ALS, and protect different organ from damages [8]. The cytoprotective effects of EDA can be exploited to prevent from myocardial, retinal, lung, intestinal, liver, pancreatic and renal injuries [78]. It is therefore logical to note the potential interest of EDA in cancer, which is also frequently associated with an oxidative stress. The antiproliferative effects of EDA are relatively modest, alone or in combination with other drugs, and of limited interest. This is not surprising for a drug primarily endowed with cell protective effects. However, there may be an interest to combine EDA with irinotecan to combat metastases to the central nervous system, which are associated with considerable mortality in patients with cancer. In sharp contrast, the capacity of EDA to protect from damages induced by oxygen radicals is much more pertinent in oncology. Many chemo and radio-therapeutic anticancer treatments involve reactive oxygen/nitrogen species to block the cancer cell metabolism (DNA damages, lipid peroxidation, mitochondrial perturbations). EDA can be useful to limit the damages induced by cytotoxic drugs in non-tumoral tissues, notably to lessen the nephrotoxic or ototoxic effects of cisplatin, to reduce the cardiotoxicity of anthracyclines or to diminish the side effects of radiotherapy, as described above. Similar protective effects have been evoked with other scavengers of ROS. For example, the hydroxyl radical scavenger dimethylthiourea has been shown to prevent the renal damage caused by cisplatin [79]. Another antioxidant, protocatechuic acid (3,4-dihydroxybenzoic acid) which is abundant in green tea, protects against nephrotoxicity induced by doxorubicin [80]. Other compounds could be cited but the advantage of EDA is that it is a drug with a proven safety after 18 years of use in Human as a modulator of free radical scavenging pathways in brain-related diseases. As a drug already authorized for use in Humans, its applications could be more easily extended to cancer-related conditions.

Another major advantage of EDA is its capacity to cross the blood–brain barrier, to diffuse into the central nervous system and to act on the cerebral vasculature and neuronal networks, offering a potent neuroprotection. Therefore, the drug is well adapted to combat the neurotoxicity of cisplatin and cyclophosphamide, as described above but possibly also the neurotoxic effects of other established anticancer drugs like the taxanes (e.g. paclitaxel) and vinca-alkaloids (e.g. vincristine). EDA is a remarkable anti-oxidative and anti-inflammatory drug. It functions as a NFκB inhibitor and Nrf2 activator, like for examples the cytoprotective and anticancer phytochemicals resveratrol, curcumin, epigallocathechin-3-gallate and sulforaphane [81,82]. The polyphenol honokiol, the main active ingredient from the bark of *Magnolia officinalis*, also exhibits anticancer and neuroprotective activities [83,84]. It functions as a potent ROS scavenger and promotes nuclear translocation and activation of Nrf2 and displays potent neuroprotection against oxidative stress-mediated cell damage [85]. Its mode of action resembles that of EDA.

The potential interest of EDA to mitigate autoimmune thyroiditis is very interesting in the context of cancer therapy with immune checkpoint inhibitors. Therapeutic antibodies targeting the PD-1/PD-L1 pathway have revolutionized the treatment of specific cancers, notably non-small cell lung cancer and melanoma, but they also induce life-threatening toxicities. Autoimmune thyroiditis induced by antibodies that block the interaction between PD-1 and PD-L1 is frequently observed in cancer patients [86]. It can lead sometimes to irreversible thyroid dysfunctions. Interleukin (IL)-17 (a hallmark cytokine of T-helper 17 cells) plays a significant role in the pathogenesis of autoimmune thyroid diseases, in particular Hashimoto's thyroiditis [87] and EDA has the capacity to inhibit expression of IL-17 implicated in the destruction of thyrocytes [48]. The use of EDA in the therapy of autoimmune thyroiditis induced by anti-PD-1/PD-L1 antibodies could be important. It is interesting to note that the anti-inflammatory and antimalarial natural product dihydroartemisinin (DHA) has also been found to attenuates autoimmune thyroiditis [88]. For both EDA and DHA, the

STAT3/PI3K/Akt pathway was found to be implicated in the process. The use of EDA to prevent from or to alleviate cancer immunotherapy-induced autoimmune thyroiditis no doubt merits further studies. The therapeutic impact can be very significant.

Collectively, the information reviewed here clearly suggest that EDA can play a role to support cancer treatments. One of the limitations of EDA is its very low aqueous solubility (and solubilization in vehicle and intestinal fluids) which is the primary determining factor for its intestinal absorption [89]. This limitation imposes a parenteral administration of the drug, whereas oral administration would be preferable for the use in chronic diseases and cancer. Novel oral and sublingual tablet formulations of EDA are investigated currently to improve its oral bioavailability. The results look promising [90–93]. Formulations to facilitate the brain delivery are also investigated [3]. They could be useful for the treatment of brain tumors or metastases. A future for EDA in cancer can be envisaged.

Declaration of Competing Interest

The author declares no conflict of interest.

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