Anticancer Drugs and Amyotrophic Lateral Sclerosis

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Contributor: Rosa Luisa Potenza , Monica Armida , Patrizia Popoli

Amyotrophic lateral sclerosis (ALS) is a rare progressive motor neuron disease that, due to its high complexity, still lacks effective treatments. Development of a new drug is a highly costly and time-consuming process, and the repositioning of approved drugs can represent an efficient strategy to provide therapeutic opportunities. This is particularly true for rare diseases, which are characterised by small patient populations and therefore attract little commercial interest. Based on the overlap between the biological background of cancer and neurodegeneration, the repurposing of antineoplastic drugs for ALS has been suggested.

amyotrophic lateral sclerosis | anticancer drugs | repositioning

1. Introduction

Amyotrophic lateral sclerosis (ALS) is a rare neurodegenerative disease characterised by selective damage to upper and lower motor neurons, leading to death, usually as a consequence of respiratory failure, approximately 3–5 years after symptom onset [1][2]. The prevalence of ALS has been reported as between 4.1 and 8.4 per 100,000 and it is expected to grow, mainly due to the ageing population [3].

The pathophysiological mechanisms underlying the disease are still poorly understood [4]. As is the case with other neurodegenerative diseases, ALS genesis appears to be regulated from a complex interaction between individual genetic risks, aging and environmental factors [5]. More than 90% of ALS cases are sporadic, whereas about 5–10% are familial [1]. About 60% of familiar and 10% of sporadic ALS cases are due to pathogenic mutation in superoxide dismutase 1 (SOD1), TAR DNA-binding protein (TARDBP), fused in sarcoma (FUS) and chromosome 9 open reading frame 72 (C9orf72), the four most common ALS-associated genes [6].

Many ALS patients also show cognitive disturbances, extrapyramidal deficits and neuropathological findings, which reveal the multisystem nature of the disease [7]. Such a multifactorial nature partially explains why, in spite of intense basic research efforts, effective treatments remain elusive and ALS still represents an unmet medical need. Indeed, currently only two drugs, riluzole and edaravone, have currently received marketing authorisation for ALS treatment; moreover, their efficacy is rather limited [8].

The discovery of a new drug is a highly costly and time-consuming process, and the propensity of pharmaceutical companies to allocate their resources depends on the commercial potential of the future drug. Thus, in the case of rare diseases, the interest of private industry is often limited. The repositioning of drugs already approved for

alternative indications could represent an efficient strategy to provide therapeutic opportunities for orphan diseases [9]. The advantages of this approach vs. de novo drug development are obvious. Indeed, for approved drugs, pharmacodynamics, pharmacokinetics and safety in the clinical setting are already established, making the research process quicker and less costly, subsequently allowing their rapid implementation into new medical applications. Repositioning may typically be considered when a drug acts on a pathogenetic mechanism that is shared by different diseases. From a more complex point of view, repositioning may rely on the “promiscuous” nature of the drugs, as they often interact with multiple targets, each of which may have a role in the pathogenesis of different diseases [10].

Some evidence has highlighted the existence of intriguing relationships between neurodegeneration and cancer [11][12]. In particular, despite the opposite hallmarks of the two conditions (excessive cell proliferation vs. cell loss), it has been suggested that some anticancer drugs might be repurposed for the treatment of neurodegenerative diseases, including ALS [13][14]. In agreement, researchers proposed in a previous article that fenretinide, an analogue of retinol endowed with antineoplastic activity, could additionally be considered as well for the treatment of ALS and other neurological disorders [15].

As far as ALS is specifically concerned, its possible interconnections with cancer have been explored by several studies supporting mutual links between these two age-related diseases [16]. Indeed, microarray analysis of ALS patient samples showed that candidate genes for ALS biomarkers are related to cancer development [17][18][19]. Other studies revealed common signalling pathways between ALS and cancer, such as Scr/c–abl, which was found to be overactivated during both cancer and ALS progression [20], and the P38 mitogen-activated protein kinase (p38MAPK) pathway [21], whose inhibition rescued the axonal transport defects in ALS mice [22].

Epidemiological studies on the possible association between cancer and ALS have reported discordant results. Fang et al. [23] reported no overall association of cancer and risk of ALS, while more cases of some specific tumours (specifically, prostate and brain) were diagnosed in ALS patients. Freedman et al. [24] reported that ALS mortality was not associated with total cancers, while the risk of ALS death was found to be increased or decreased when specific tumours were considered. Moreover, a longitudinal study showed a reduced overall risk of cancer, but an increased risk for salivary and testicular cancer, in ALS patients [25].

Such discrepancies may well be explained by the fact that speaking in terms of “cancer” as though it were a single disease can be misleading, since even cancers with the same histological origin can dramatically differ from one another in terms of clinical, prognostic and therapeutic issues according to their specific molecular profiles. Similarly, “anticancer drugs” is an umbrella term including very different molecules (and related mechanisms of action) that should not be regarded as a whole.

2. Miscellaneous

Fenretinide (DrugBank Accession Number DB05076, N-(4-hydroxyphenyl)retinamide) is a semisynthetic derivative of all-trans retinoic acid produced in the USA in the 1960s and was first proposed as an anticancer treatment due

to its significant antitumour activity and favourable toxicological profile [26]. The antitumour effect of fenretinide is very complex and includes different mechanisms of action [15].

Even if it has not yet been approved by the EMA, fenretinide obtained orphan designation by the European Commission for the treatment of primary malignant bone tumours [27] and cutaneous T-cell lymphoma [28].

Very recently, researchers demonstrated that low doses (10 mg/kg) of a new fenretinide formulation significantly attenuates the neurological phenotype and extends the survival of mice expressing the mutated form of human SOD1 protein (mSOD1^{G93A} ALS mice), even when administered after the onset of motor symptoms [29]. They also demonstrated that in cultured motoneurons the expression of ALS-linked SOD1 mutation resulted in mitochondrial dysfunction, which can be reversed by treatment with fenretinide. The ability of FEN to protect myotubes from “in vitro” mSOD1 toxicity could partially explain the attenuation of the progression of neurological symptoms observed in mSOD1^{G93A} mice chronically treated with the drug [29].

The results extended the neuroprotective potential of this anticancer drug to ALS treatment already reported for other neurological diseases like multiple sclerosis and Alzheimer’s disease [15]. The neuroprotective effects of fenretinide occurred at much lower doses than those required for its antitumour activity. Indeed, high doses of fenretinide can activate acute responses leading to ROS increase and cell death [30], while, at subtoxic concentrations, the drug can stimulate an adaptive stress response [31].

3. Alkylating Agents

The platinum complexes have revolutionised cancer therapy and the majority of chemotherapic regimens routinely applied in the clinical setting are still platinum-based [32]. These inorganic compounds are classified as alkylating agents and are used in the treatment of different forms of cancer, including sarcomas, carcinomas, lymphomas and germ cell tumours [33].

Cisplatin (DrugBank Accession Number DB00515) was the first member of its class, which now also includes carboplatin and oxaliplatin. As with all the other alkylating agents, cisplatin prevents the cell from dividing by adding an alkyl group to the DNA. However, only a small fraction of the administered dose reacts with the DNA to induce cytotoxicity, whereas the largest amount binds cellular proteins, thereby influencing other potential targets [34]. Calderone et al. showed that cisplatin selectively binds to His-19 residue located on the surface of the bovine SOD protein Cu/Zn superoxide dismutase (SOD1) [35]. SOD1 is an antioxidant enzyme that catalyses the dismutation of superoxide radicals; approximately 20% of familial ALS (FALS) cases are due to mutations in the SOD1 gene and, albeit at a very low frequency, SOD1 mutations are also observed in the sporadic form of the disease (SALS) [36]. Furthermore, not only the mutation but also the aggregation of the wild type SOD1 protein may play a role in modulating disease initiation [37]. In 2012, Banci and colleagues showed that cisplatin also interacts with the human form of SOD1, binding two cysteines (Cys6 and Cys111) onto the protein surface [38]. Cys6 and Cys111 residues were implicated in the aberrant aggregation of the mutated form of SOD1 [39], which are deemed to be essential in

inducing endoplasmic reticulum (ER) stress related to SOD1 protein misfolding in ALS [40]. The potential use of cisplatin in the treatment of ALS was thus proposed [41].

Carboplatin (DrugBank Accession Number DB00958) is another platinum-based drug already approved to treat different forms of cancer. Due to its hydrophilic nature, carboplatin is longer retained longer within brain tissue; interestingly, it was found to be highly effective against glioblastoma while being nontoxic to normal brain tissue [42]. In breast cancer cells, carboplatin induced the expression of the omega class of cytosolic glutathione S-transferase (GSTO1) [43], an enzyme that is significantly reduced in peripheral blood mononuclear cells and in the spinal cord from ALS patients [44]. The glutathione S-transferase omega 1 (GSTO1) and 2 (GstO2, the Drosophila homolog of human GSTO1) were found to be involved in the oxidative damage underlying the pathogenesis of neurodegenerative diseases [45]. The overexpression of GSTO was shown to reduce the citoplasmatic accumulation of two proteins whose abnormal aggregations are characteristics of ALS and frontotemporal dementia [46], namely, the fused in sarcoma (FUS) DNA/RNA-binding protein and the Transactive response DNA-binding protein-43 (TDP-43) [47]. Specifically, Cha et al. showed that FUS neurotoxicity is sustained by impaired protein solubility induced by glutathionylation and that the overexpression of glutathione transferase omega 2 (GstO2) reduces abnormal protein aggregates in both TDP43 and FUS transgenic *Drosophila*, thus highlighting the therapeutic potential of carboplatin in ALS. Indeed, the drug rescued the mitochondrial disfunction and dose-dependently reduced locomotor and eye deficits in the FUS-ALS fly model [48].

4. Antimetabolites

Antimetabolites are nucleoside analogues interfering or competing with nucleoside triphosphates in the synthesis of DNA (antimitotic) or RNA or both. The fluoropyrimidine 5-fluorouracil (5-FU) (DrugBank Accession Number DB00544) is a pyrimidine analogue used as a palliative cancer treatment or to treat basal cell carcinomas. Besides its antimitotic effect, 5-FU can also induce striking alterations in RNA metabolism, splicing and post-transcriptional modification [49], suggesting the possible occurrence of several off-target effects. In a preclinical study designed to evaluate stem cell mobilisation in the murine ALS model, Rando et al. administered 5-FU as a negative control. As expected for an anticancer drug, the 5-FU administration induced a reduction of cellular component with a rapid turnover, as blood cells, an effect fully recovered after two weeks of repeated treatment. Surprisingly, however, when chronically administered in the pre-symptomatic phase, 5-FU also delayed the disease onset, improved the motor performance and increased the lifespan of ALS-treated animals, while it did not exert major effects on the myogenic, apoptotic or autophagic markers commonly elevated in mSOD1^{G93A} muscles [50]. Although no mechanistic data were provided by the above study, 5-FU has been reported to reduce tryptophan-induced SOD1 aggregation in cells [51]. This can be very relevant to the possible therapeutic effects of 5FU on human ALS, since tryptophan residue at position 32 has a critical influence on human SOD1 toxicity to motor neurons [52].

5. Hormone Antagonists

Tamoxifen (DrugBank Accession NumberDB00675) is a selective estrogen receptor modulator with both estrogenic and anti-estrogenic effects. In breast tissue, tamoxifen exerts anti-estrogenic and antitumour effects by blocking estrogens from entering cancer cells and thus reducing or eliminating the cells' ability to grow and spread [53]. It is generally used to treat breast cancer in men and women and as a prophylactic treatment against breast cancer in women. Besides its antitumour activity, tamoxifen also showed neuroprotective effects in some preclinical models of neurological disease [54]. In experimental brain injury, the drug reduced neuroinflammation through TLR4/NF-kappaB pathways [55], while in a murine model of spinal cord injury it reduced microglia activation and the apoptotic death of neural cells [54][56]. Interestingly, in mice overexpressing TDP-43 DNA/RNA-binding protein (identified as the major component of the cytoplasmic inclusions in frontotemporal dementia and ALS), tamoxifen treatment was associated with an improvements in motor functions. The behavioural effect was accompanied by a reduction in the neuronal loss and TDP-43 inclusion in the forebrain of mice. Furthermore, in this murine model, tamoxifen also increased MTOR-dependent autophagy through AKT/PKB inhibition [56]. On the basis of the above results, a placebo-controlled randomised clinical trial was conducted in ALS patients without mutations in superoxide dismutase-1 (SOD1) or fused in sarcoma (FUS) genes [57]. Tamoxifen only modestly attenuated disease progression without exerting any significant effect on the primary clinical endpoint (time to death or dependence on mechanical ventilation, and tracheostomy with continuous mechanical ventilation and noninvasive ventilation for more than 12 h per day). This study must, however, be considered inconclusive; due to the extremely limited sample size (10 patients on tamoxifen and 8 on placebo), it was dramatically underpowered to detect a statistical significance in the clinical endpoint. Considering both the preclinical evidence and the inverse correlation between tamoxifen treatments and ALS risk reported in a population-based case–control study of >10,000 US cases [58], the potential therapeutic role of tamoxifen on human ALS seems worthy of further investigation in larger clinical studies.

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