Proteasome inhibitors / Antabuse (Disulfiram)

Year 1977

Several scattered clinical observations testify to the possibility that **Disulfiram** (trade name ***Antabuse***) is able to suppress some oncological diseases. In one landmark article from 1977 [1] , Dr. E.F. Lewison of Johns Hopkins Hospital (https://www.hopkinsmedicine.org/the_johns_hopkins_hospital/index.html) describes the case of a woman who was operated on for aggressive **breast cancer** in 1956 at the age of 35. Three years later, she developed severe back pain, the cause of which turned out to be extensive metastases in the spine, ribs and pelvic bone. In 1961, the patient became an alcoholic and had to take disulfiram (*Antabuse*). Over the next ten years, all metastases completely disappeared. The woman died in 1971 as a result of falling out of the window while heavily drunk, but from an oncological point of view she was perfectly healthy. Lewison speculated that the **anticancer activity** of disulfiram (*Antabuse*) was due to its underlying **ability to inhibit the enzyme acetaldehyde dehydrogenase**.

Dithiocarb

At the turn of the 80s – 90s of the 20th century, a substance called **dithiocarb** (*Sodium diethyldithiocarbamate (https://www.sciencedirect.com/topics/agricultural-and-biological-sciences/sodium-diethyldithiocarbamate)*) (also called **immuthiol** in the Czech Republic) became popular. This substance is created in the body from disulfiram (*Antabuse*) after its ingestion and is characterised by high reactivity. Among its other effects, it is able to react with copper contained in the blood and form a complex, which we denote by the abbreviation **CuEt**.

Effect on HIV

Dithiocarb was believed to be able to have a beneficial effect on the immunity and thus could be a suitable drug against **HIV/AIDS**. Some clinical tests published in prestigious medical journals (Lancet (https://secure.jbs.elsevierhealth.com/action/getSharedSiteSession?redirect=http%3A%2F%2Fwww.thelancet.com%2F&rc=0&code=lancet-site), JAMA (https://jamanetwork.com/)) showed the miraculous effectiveness of dithiocarb against this disease. However, further clinical trials failed, and when dithiocarb was found to have **no effect on the immunity of HIV/AIDS patients**, the whole story fell into oblivion. The success of clinical trials of dithiocarb against HIV/AIDS has remained unexplained to this day. However, it seems that its effectiveness could be significantly influenced by the amount of copper in the patients' diet and was not related to the effect on immunity at all, but to the **ability of CuEt to inhibit the proteasome**[2].

Effect on breast cancer

However, it is important for us that dithiocarb was also used in a clinical trial on 64 patients (phase 2) with breast cancer (independently of *Lewison*) during its glory days. The results were very positive: after six years, 81% of the patients in the dithiocarb group were alive, while only 55% of the patients[3] in the placebo group were alive. The authors based this test on the assumption that dithiocarb positively affects the immune system. However, when this assumption turned out to be wrong, the data obtained stopped making sense and further research was abandoned.

On the grounds on the University of Utah

Then **disulfiram** (*Antabuse*) began to force itself back into the spotlight of human history through experiments conducted by **Professor T. P. Kennedy**'s group at the University of Utah (https://www.utah.edu/). Independently of the two publications already mentioned, these researchers discovered that **disulfiram** (*Antabuse*) has strong antitumor activity when it **forms complexes with metals**, especially **zinc and copper**. They decided to apply their results to a hopelessly ill patient with a large melanoma metastasis in her liver. The patient was taking **disulfiram** (*Antabuse*) and ***zinc gluconate***, each separately, daily. After three months, the metastasis disappeared and there was a full recovery of health, so that no more hospitalization was required. Until the results were published in 2004, the woman had lived with a daily dose of disulfiram (*Antabuse*) and zinc for 55 months without any deterioration in her health[4]. However, the reason for this remarkable antitumor activity was difficult to find until the discovery made by **Professor Q. P. Dou in Detroit (Michigan)** with his team. Experiments in his laboratory showed that **CuEt is a strong inhibitor of the proteasome**, even *in vivo* in mice, where it effectively suppressed xenografts derived from a human breast tumor line[5].

CuEt clinical trials

The results of the two **American** teams then resulted in a clinical test at the Huntsman Cancer Institute in Utah (https://healthcare.utah.edu/huntsmancancerinstitute/), which began in the summer of 2008 and continues to this day (the investor is the *University of Utah*). In this trial (phase 1), patients with liver tumors (primary and secondary, with or without origin determination) are given oral and daily **disulfiram** (*Antabuse*) and **copper gluconate**, each separately. If disulfiram (*Antabuse*), potentiated with copper, works so strongly against solid tumors, it seems likely that it will inhibit the proteasome in some way other than bortezomib (trade name *Velcade,* also a proteasome

inhibitor). The mode of inhibition of the proteasome by CuEt is now the really exciting question. CuEt has recently been shown to be unable to inhibit the 20S proteasome and is much more likely to target Poh1 in the lid of the 26S proteasome[6]. However, the mechanism of the antitumor effect of CuEt, which is produced in our body after ingestion of disulfiram (*Antabuse*) or **dithiocarb**[7], is still a much bigger question than the mechanism of action of bortezomib.

Links

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