The A-DAC Principle: A New Concept in Oncology Treatment

What is the A-DAC Principle?

The A-DAC (alkylating deacetylase) principle is a new approach in chemotherapy that uses **fusion molecules** to combine an alkylating moiety with a pan-histone deacetylase (HDAC) inhibitor within the same treatment to simultaneously damage DNA and block damage repair.[1,2,3]

This is a departure from the traditional method of combining several chemotherapy agents with different modes of action in order to improve efficacy, often resulting in increased toxicity.[1] The A-DAC principle was designed to combine chemotherapy with a targeted approach in one molecule to create synergy and to increase efficacy without compromising tolerability.[1]

What is a Fusion Molecule?

Fusion molecules combine two validated anti-cancer modes of action in one molecule in order to synergise and improve upon the efficacy of the single agents. Ideally, these include a chemotherapy and a targeted agent fused into one molecule.[4]

EDO-S101 is a representative of the A-DAC principle, and combines the active moieties of the alkylating agent and the HDAC inhibitor through fusion technology.

When used in malignant cells:[1]

- **Alkylating agents** cause breaks in the DNA that result in cell death[2]
- **HDAC** inhibition suppresses gene transcription and prevents the growth of cancer cells and may influence control mechanisms that protect against cell death.[3]

Rationale for Development

A fusion molecule offers true bi-functionality and synergy in antineoplastic activity.[5,6]

The A-DAC principle was proposed to exploit a synergistic mode of action that may overcome the difficulties associated with the combined use of two separate entities.[1]

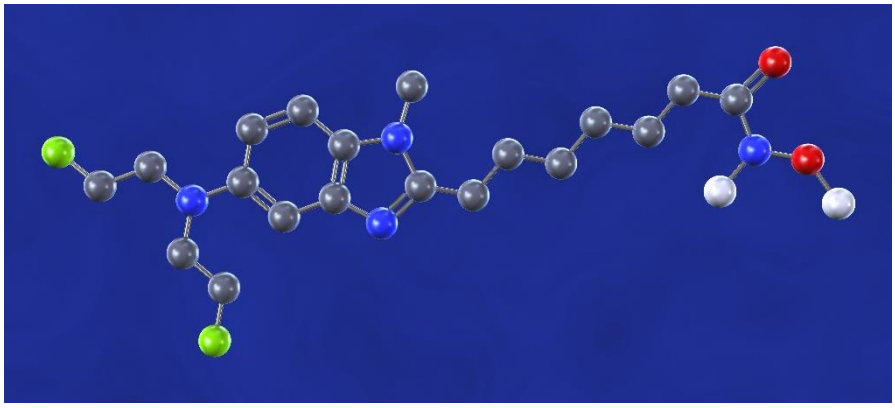
Successful treatment of cancer is often hindered by the development of resistance to the therapy. HDAC enzymes are overexpressed in some cancers inducing cell proliferation and resistance.[1,5]

A-DAC Fusion Molecule

The new chemical entity, EDO-S101, is the fusion of bendamustine with vorinostat.[1] Both are well established anticancer agents with extensive properties.[2,3] Bendamustine has been shown to regulate pathways for DNA repair and cell death, while vorinostat blocks the cell cycle and division preventing further growth in a broad spectrum of cancer cells, with little toxicity to normal cells.[2,3]

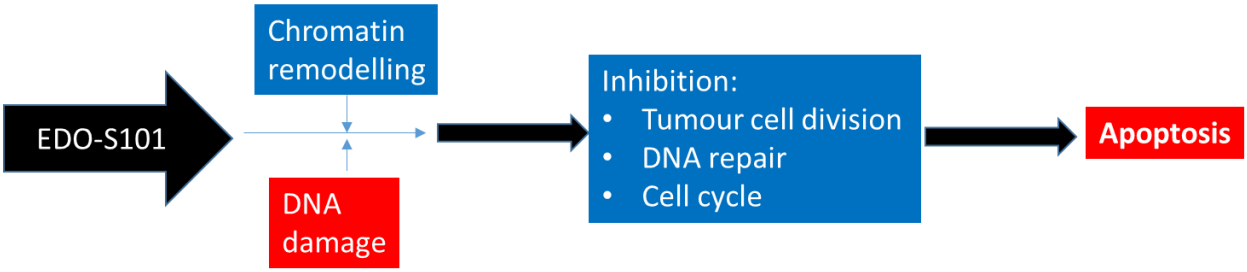
The rationale for designing this molecule is based on two assumptions currently under investigation in a clinical study:

- Chromatin is the functional and structural unit of DNA. It is very tightly coiled in its normal state, but is relaxed by HDAC inhibition.[1,7] It is anticipated that vorinostat may make DNA more accessible to the damaging effects of bendamustine.[1]
- Once the DNA is damaged, vorinostat may impair the ability of cancer cells to repair this DNA damage.[1]



Mode of Action

On intravenous administration, EDO-S101 targets and binds to HDAC resulting in chromatin remodelling, modulation of gene expression, inhibition of tumour cell division and induction of cell apoptosis.[4] It also causes DNA fragmentation and cell-cycle arrest resulting in cell death.[4,8] EDO-S101 induces inositol-requiring enzyme activity and subsequent production of key regulatory proteins that increase cancer cell sensitivity to some other chemotherapy agents.[4]



Pre-clinical Results

Initial investigations with EDO-S101 *in vitro* and *in vivo* show that the full function of both molecules has been retained. Repair proteins are less abundant following a strong DNA damage response, and cell death is triggered at lower concentrations of this fusion molecule than with bendamustine alone.[1]

This bi-functional mode of action appears superior to the independent activity of each agent exhibiting a synergy with the result that EDO-S101:[1,8]

- Induces cell cycle arrest
- Causes potent DNA damaging effects
- Impairs DNA repair via homologous recombination.

Furthermore, in myeloma cells isolated from patients, EDO-S101 was able to overcome resistance to alkylators, such as melphalan, and potentiated the activity of agents such as dexamethasone, lenalidomide and proteasome inhibitors.[8,9]

In mice, EDO-S101 showed a more sustained anti-tumour effect than bendamustine and vorinostat given individually or concomitantly.[9]

Clinical Investigation

It is anticipated that the A-DAC, EDO-S101, may have strong activity in haematological and solid malignancies.[4]

The first clinical study in patients with relapsed/refractory haematological malignancies will evaluate the efficacy, safety and pharmacokinetics of EDO-S101.[9]

References

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