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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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:\textsuperscript{1}

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

Rationale for Development
A fusion molecule offers true bi-functionality and synergy in antineoplastic activity.\textsuperscript{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.\textsuperscript{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.\textsuperscript{1,5}

A-DAC Fusion Molecule
The new chemical entity, EDO-S101, is the fusion of bendamustine with vorinostat.\textsuperscript{1} Both are well established anticancer agents with extensive properties.\textsuperscript{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.\textsuperscript{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.\(^5\)

**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**