The Evolution of Chemotherapy: Using the A-DAC Principle to Unlock New Treatment Options in Hodgkin Lymphoma

A Summary of the: Mundipharma EDO Satellite Symposium
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Introduction
Dr Volker Diehl, MD, PhD
Director Emeritus for Internal Medicine
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Dr Diehl welcomed the audience and introduced the concept of the fusion molecule, which places two established modes of action into one molecule rather than using separate therapies in combination. In exploring the rationale for the new fusion molecule EDO-S101, he explained that compared with using combination therapy they would: “hopefully get an increase in efficacy and lower the toxicity.”

The Evolution of Chemotherapy
Dr Volker Diehl, MD, PhD

Radiotherapy had been the mainstay of treatment until the 1950s and 1960s and chemotherapy was developed from the unmet need to eliminate all clonogenic cancer cells and cure the patient. Dr Diehl described the journey from the development of increasingly complex and toxic treatment protocols, through the search for analogues with lower toxicities, to the introduction of major types of chemotherapies available today, such as taxanes and topoisomerase I inhibitors. He then focused on more recent developments where researchers have explored the driving force behind the progression of normal cells to those that are malignant to enable them to identify and target new treatment pathways. However, the very nature of cell proliferation and adaptation has facilitated the development of resistance to these treatments. This has been confounded by the dose-limiting effects of the associated toxicity.

Combination therapies for Hodgkin lymphoma
The advent of notable combination chemotherapies began in the 1960s with the four drug-principle: MOPP (mustargen, oncovin [vincristine], procarbazine, and prednisone), which was superseded by ABVD (adriamycin [doxyrubicin], bleomycin, vinblastine, and dacarbazine) in the 1970s. Subsequent progress made by the German Hodgkin Study Group, facilitating dose-density as well as dose-intensity, resulted in the seven-agent BEACOPP (bleomycin, etoposide, adriamycin, cyclophosphamide, oncovin, procarbazine, and prednisone) regimen in the 1990s; an effective treatment, but with a high toxicity.

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Dr Volker Diehl, MD, PhD

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Professor Antonello Pinto, MD

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Professor Dr Christoph Driessen, MD

The A-DAC Principle: Unlocking the Potential
Dr Volker Diehl, MD, PhD
Dr Diehl explained that multi-drug resistance from oncogenic mutations is often due to the suppression of apoptosis in DNA-damaged cells. The ongoing investigations aimed at preventing such resistance use molecular therapies, such as p53 gene therapy or inhibition of the P13-kinase pathway.

This has evolved in recent years from targeted chemotherapies, such as brentuximab vedotin, to immunotherapy in which the patient’s own immune system is stimulated via antibody-mediated blockade to activate the T-cells and induce apoptosis. Dr Diehl observed that today, tumour-free survival rates in Hodgkin lymphoma, may be as high as 90% to 95% and observed that while the golden age of chemotherapy may be over, that: “cytotoxic chemotherapy is staying on and we will use it as comparator…for any new development.”

**The fusion molecule**

On announcing the advent of the fusion molecule EDO-S101, Dr Diehl considered the avenues opened for future treatment by combining two validated anti-cancer modes of action in one molecule. He explained that the break in DNA that leads to cell death caused by the alkylating agent bendamustine may be reinforced by the histone deacetylase inhibition (HDACi) of gene transcription with vorinostat, thereby influencing the mechanisms that control cell death.

Importantly, it is hoped that this synergistic approach may make DNA more accessible to the damaging effects of bendamustine while impairing repair within the cancer cell. Ultimately, Dr Diehl observed that the fusion molecule EDO-S101 has a high affinity to DNA and rapid crosslinking.

**References:**

Over the last two decades, bendamustine has been a breakthrough drug and Professor Pinto presented evidence of its effect in Hodgkin lymphoma where overall response rates of up to 58% have been observed in patients with relapsed refractory disease along with a complete response rate of 29%–35%.¹,²

Professor Pinto noted that the problem in treating Hodgkin lymphoma arises with primary resistance to bendamustine and also because patients develop resistance to the agent during treatment. He then considered vorinostat, the first in class HDACi, which displays clinical activity in refractory Hodgkin lymphoma concluding that together these properties made Hodgkin lymphoma an ideal model in which to test EDO-S101.

EDO-S101 was first tested in a wide panel of Hodgkin lymphoma cell lines and Professor Pinto revealed that he and his colleague Professor De Filippi were: “surprised to find that EDO-S101 displays a very strong cytotoxic activity to practically all Hodgkin lymphoma cell lines, but what is interesting is that the IC50 for this agent is at least 10-fold lower than observed with bendamustine.” He went on to explain that EDO-S101 was not the addition of two molecules, but an entirely new molecule with properties that are different from those of both bendamustine and vorinostat.

EDO-S101’s IC50:
“At least 10-fold lower than bendamustine”

Professor De Filippi developed the R100 cell line from the Hodgkin-Reed/Sternberg Cell Line L1236 to be resistant to bendamustine concentrations of 100µM or more — higher than is observed in patients treated with 90 mg/m². Importantly, EDO-S101 showed greater cytotoxicity against R100 cells than either bendamustine or vorinostat.³

EDO-S101 in bendamustine-resistant Hodgkin lymphoma⁴

EDO-S101 triggers different gene expression from bendamustine and downregulates cell check points activated by bendamustine exposure, which may make it suitable for combination with check point inhibitors in the future. RNA data was used to make the point that in both bendamustine-naïve and -resistant cells, EDO-S101 downregulates genes related to metastatic catastrophes, as well as those associated with acquired resistance to alkylators, such as bendamustine. Functionally, this redirects the cell towards a pathway for cell death. In addition, EDO-S101 upregulates other genes that lead to apoptosis.³

Unlike vorinostat, EDO-S101 did not downregulate CD30 in parenteral Hodgkin lymphoma cell lines and its combination with brentuximab vedotin reduced cell survival in both naïve and bendamustine-resistant cells; more than with each agent individually.³

Professor Pinto went on to highlight that the ability of EDO-S101 to overcome resistance is not unique to Hodgkin lymphoma cell models and that it is also able to induce a cytotoxic effect in multiple myeloma cell lines selected for resistance to melphalan.⁴

Indeed, in pre-clinical models of an aggressive transplanted multiple myeloma tested against commonly used agents with anti-myeloma activity, EDO-S101 was the only agent...
able to reduce the ‘M-spike’, indicating that the properties of EDO-S101 are not confined to Hodgkin lymphoma. Professor Pinto concluded that EDO-S101 has a potent cytotoxic activity towards a variety of Hodgkin lymphoma cell lines at concentrations 10-times lower that required with bendamustine, it is effective in bendamustine-resistant cells and it has the potential for synergy with brentuximab vedotin, and may be suitable for treating a variety of haematological malignancies.

References:

“Striking effect against bendamustine-resistant Hodgkin lymphoma cells”

Pre-clinical multiple myeloma evaluation
EDO-S101 has been shown to be effective in pre-clinical data against multiple myeloma cell lines,1 and Professor Driessen focused specifically on the use of alkylators, noting that EDO-S101 showed greater cytotoxicity against myeloma cells than melphalan, cyclophosphamide or bendamustine. Furthermore, when combined with the proteasome inhibitor bortezomib, EDO-S101 demonstrated greater cytotoxicity than bortezomib with vorinostat or bendamustine alone. 

Analytical simulation combining EDO-S101 with either bortezomib or carfilzomib produced synergistic combination indices across a wide range of multiple myeloma cell lines, particularly in those that are proteasome-inhibitor resistant.

Activity in AMO myeloma: 1-hour pulse treatment

“Blocking the cell from repairing the damage we have done by chemotherapy”
synergy with proteasome inhibitors overcoming resistance. In addition, antigenic presentation increases and EDO-S101 interferes with protein catabolism.

**EDO-S101: Initial clinical findings**

The Phase I dose-escalation study explores the safety, efficacy and pharmacokinetics of EDO-S101 in patients with relapsed/refractory haematological malignancies. Professor Driessen reported patient recruitment to the first two dosing cohorts, including those with Hodgkin lymphoma (1), multiple myeloma (2), and non-Hodgkin lymphoma (3).

To date, EDO-S101 has been well tolerated, with no Grade 2 or 3 adverse events and only one event of Grade 2 thrombocytopenia.

Professor Driessen concluded that EDO-S101 was the first representative of a new approach to chemotherapy. He emphasised the encouraging effect on malignant B cells and multiple myeloma and the promising tolerability found at initial dose levels in the ongoing clinical trial.

**References:**


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**Poster Session**

**In-Vitro and In-Vivo Pre-clinical Activity of a First in Class Alkylating HDAC Inhibitor Fusion Molecule (EDO-S101) in Hodgkin Lymphoma**

Evaluation of eight Hodgkin lymphoma cell lines exposed in vitro to a range of EDO-S101 doses, demonstrated a high sensitivity to EDO-S101 across all cell lines, inducing cell death by both mitosis and apoptosis. Fluorescence staining and histology highlighted a reduction in tumour cell infiltration post-treatment with EDO-S101. When combined with radiotherapy (6Gy), EDO-S101 increased apoptotic cell death with chromatid aberrations evident at low-doses of EDO-S101 (0.1µmol). In immune deficient mice with a L428 Hodgkin lymphoma strain xenograft, EDO-S101 reduced tumour cell infiltration and the absence of cell necrosis and degeneration compared with non-treated mice revealed an anti-tumour effect associated with EDO-S101.

**References:**

The A-DAC Principle: Unlocking the Potential
Dr Volker Diehl, MD, PhD

The A-DAC principle was defined by Dr Diehl as the fusion of an alkylating agent with an HDACi which, in the case of EDO-S101, is bendamustine and vorinostat. He highlighted the in vivo and in vitro data indicating simultaneous damage of DNA and block on its repair.

Case studies were presented for a patient with Hodgkin lymphoma and another with multiple myeloma. Both had received multiple previous treatments and had received three cycles of EDO-S101. Overall, EDO-S101 was well tolerated and an effect was observed in these highly pre-treated patients at low concentrations of the drug.

**QUESTION OF NOTE**

Why might the fusion drug appear better than the individual agents?
Dr Driessen made two observations:

- A synergistic effect is desired and when drugs with different pharmacokinetic profiles are used together their effect may peak at different times allowing only a narrow therapeutic window
- The EDO-S101 molecule has the irreversible covalent binding of bendamustine to DNA providing an anchor for intracellular HDAC inhibition

Professor Pinto noted that all biological observations showed that while EDO-S101 possessed some of the properties of the individual drugs, that new effects were also evident, so EDO-S101 appeared to be more than just the sum of bendamustine and vorinostat.