

FUSION THERAPY

a new approach to combining treatments

Increasingly, oncology agents are being used in combination. However, with complications such as drug resistance and unfavourable side-effect profiles, researchers have been looking for new ways to enhance treatment effect and tolerability. New fusion technology molecules appear to offer a beneficial synergy, but will this withstand clinical investigation and what is its future potential?

The use of systemic chemotherapy for the treatment of haematological malignancies and solid tumours relies on three established pillars; cytotoxic chemotherapy, targeted treatments and immunotherapy. In combining the use of these pillars, large steps forward have been taken in oncology. Over the last decade, chemotherapy has advanced, becoming 'smarter' and less likely to adversely affect healthy tissues. Such advances provide the real possibility of improvements in efficacy with acceptable tolerability profiles. Taken together, this results in improved patient outcomes.

The use of monotherapy in the treatment of cancer is unusual, with most agents administered as part of a combination regimen. Thus it is common to combine a cytotoxic chemotherapeutic agent with a targeted agent, such as a monoclonal antibody. In the past, the efficacy of cytotoxic combination regimens has been disappointing, with little benefit observed with intensification of dose and schedule, but an increase in the occurrence and severity of adverse events. For example,

although there is statistically significant evidence that high-dose chemotherapy in conjunction with subsequent autologous stem cell transplant improves event free survival in women with metastatic breast cancer over conventional chemotherapy, this comes at a cost of greater toxicity and no statistically significant improvement in overall survival¹. Combination chemotherapy regimens, such as CHOP (cyclophosphamide, doxorubicin, vincristine and prednisolone) for lymphoma, have become established as standard of care, however patient mortality remains high². Thus, there is a continued need for the development of more effective chemotherapeutics with acceptable tolerability profiles.

The evolution of chemotherapy

Chemotherapy has evolved significantly since the introduction of the first alkylating agents, derived from nitrogen mustard, in 1946 (Figure 1)³. Since this time, we have witnessed the introduction of combination regimens, the potential pros and cons associated with high-dose therapy, exploration of

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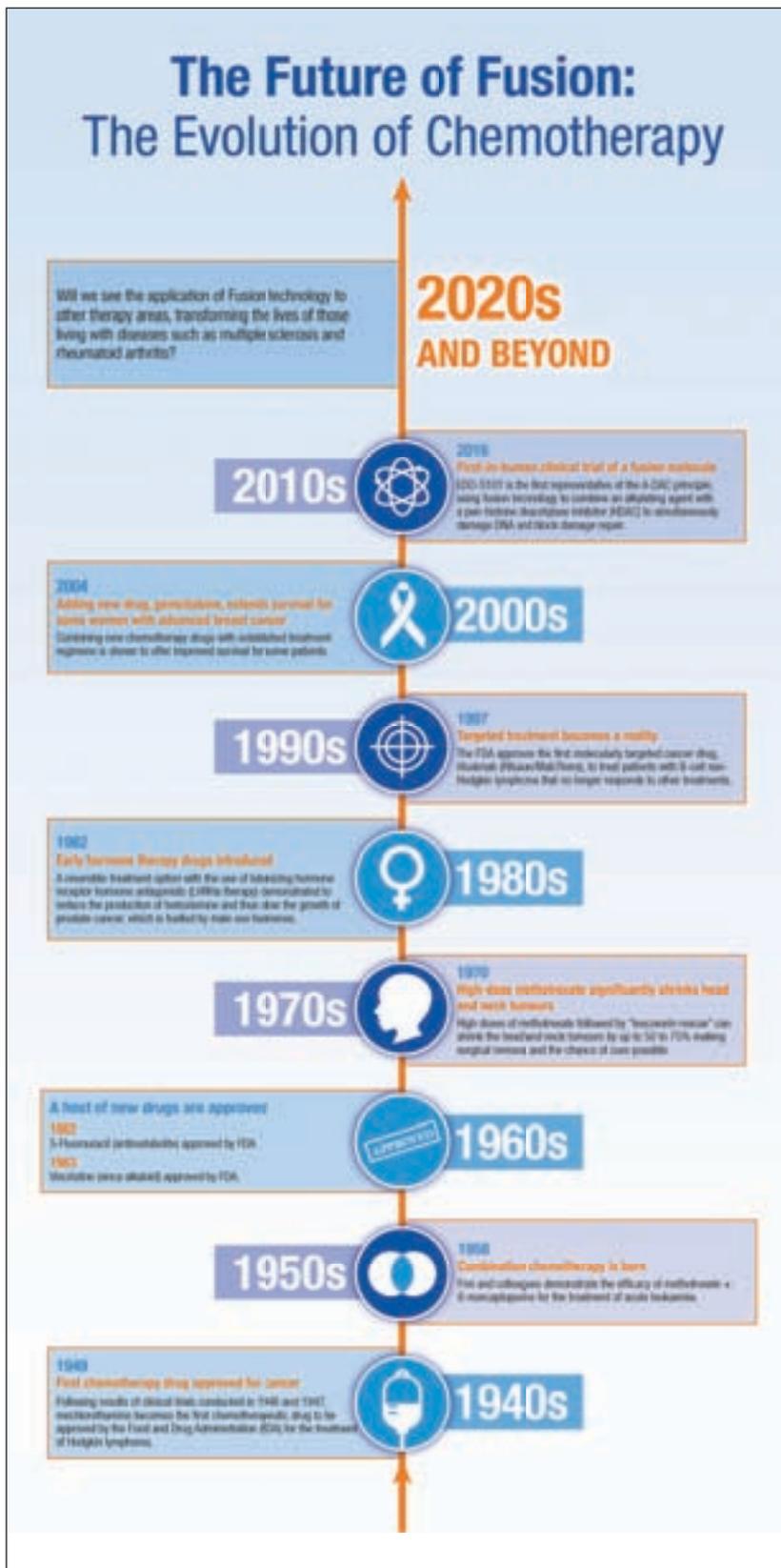


Figure 1: Timeline demonstrating the evolution of chemotherapy, from the introduction of nitrogen mustard in 1946 to the first-in-human clinical trial of a novel fusion molecule in 2016^{3,16,19-24}

hormonal therapies and, ultimately, the development of a far more targeted, selective approach to treatment.

In recent years, chemotherapy has gone from being purely cytotoxic to providing a more targeted approach to treatment. Using this approach, it has been possible to intervene in specific cellular pathways that might underlie the metastasis and growth of tumours. For example, small molecule drugs such as the protein-kinase inhibitor imatinib target the oncogene BCR-ABL tyrosine kinase. This cytogenetic abnormality, is seen in chronic myeloid leukaemia (CML) and acute lymphoblastic leukaemia (ALL), which means that treatment is more tailored to treating the disease⁴. In addition, other small molecules have been designed to target epidermal growth factor receptor (EGFR), which has been implicated in the regulation of various neoplastic processes, including cell cycle progression, inhibition of apoptosis, tumour cell motility, invasion and metastasis. For example the use of erlotinib in patients with non-small cell lung cancer (NSCLC) has improved tumour-related symptoms and increased survival⁴.

Other targeted agents that have been shown to be effective in the treatment of cancer include the monoclonal antibodies, which are designed to recognise markers carried on the surface of malignant cells. For example, the monoclonal antibody rituximab targets the CD20 molecule on the surface of B cells and was the first antibody to be licensed for the treatment of malignancy⁵. The mechanism of action of rituximab involves the depletion of malignant B cells by one of several mechanisms, which include direct antibody-dependent cellular cytotoxicity (ADCC), complement-mediated cell death and signalling apoptosis². Rituximab has been shown to induce and maintain remissions in indolent forms of non-Hodgkin lymphoma (NHL), and to improve overall survival and progression-free survival in patients with diffuse large B-cell lymphoma (DLBCL), an aggressive form of NHL².

The combination of new, targeted therapies and existing chemotherapy has resulted in considerable improvements in outcomes, and there has been speculation that the efficacy of targeted anti-cancer treatments may eventually result in classical chemotherapy becoming redundant⁶. This has been especially true for those malignancies where a single mutation may be driving disease progression.

These factors have brought classical chemotherapy to a crossroads, with serious questions posed as to its future in the modern treatment armamentarium. However, by further improving how we

combine and deliver chemotherapeutics, by continuing the evolution of chemotherapy, the role of these agents will be assured far into the future.

Fusion technology

Fusion technology represents a further step in the continued evolution of cancer treatment. This drug development strategy was created in order to enable the production of fusion molecules, which combine two validated anti-cancer agents with disparate modes of action in one molecule. By exerting their dual modes of action simultaneously, fusion molecules may overcome the difficulties of combining single agents with different pharmacokinetics and other pharmacological factors. Moreover, improvements in efficacy may be possible where combining drugs results in a synergistic mode of action⁶.

The hypothesis underlying the development of fusion molecules is that by selecting the active structures from two component agents and fusing these to produce one single molecule, it is possible to produce a new agent in which the two modes of action offer a synergy. Essentially, this new agent is able to offer a greater efficacy than either of the original components on their own, or even when they are used together as a combination therapy. In addition, fusing of the active structures from the two parent molecules ensures that both are delivered to the tumour simultaneously and are thus able to act on the tumour at the same time; something that is not always possible when combining treatments. In order to produce the ideal fusion molecule, the selected component agents should have disparate, but complementary, mechanisms of action, for example a chemotherapy agent and a targeted agent⁷. This approach has been successfully demonstrated by the A-DAC principle.

The A-DAC principle is a new approach to chemotherapy that uses fusion technology to combine an alkylating agent with a pan-histone deacetylase (HDAC) inhibitor within a single molecule to produce a treatment that simultaneously damages DNA and blocks the repair of this damage^{6,8,9}. This treatment approach departs from traditional combination chemotherapy in which several chemotherapy agents with different modes of action are given simultaneously or sequentially. Although the combination chemotherapy approach may offer improved efficacy, this often occurs at the cost of increased toxicity⁶. The A-DAC principle was designed to combine chemotherapy with a targeted approach in a single molecule in order to create synergy and to increase efficacy without compromising tolerability⁶.



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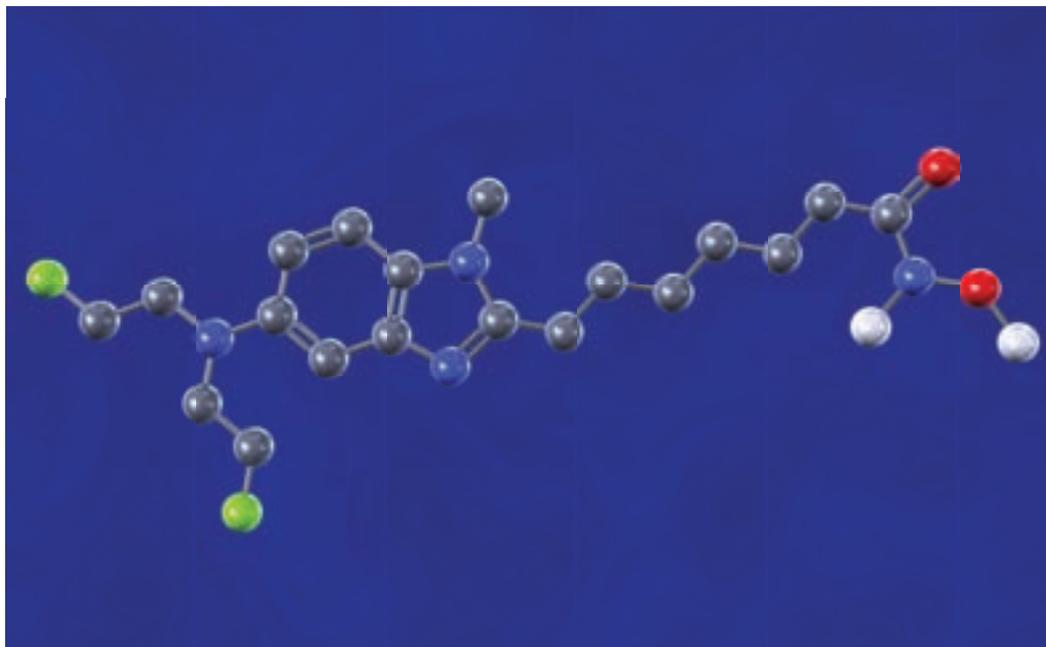


Figure 2: Structure of the first representative of the A-DAC principle, EDO-S101⁶

The new chemical entity, EDO-S101, is the first representative of the A-DAC principle (Figure 2)⁶. EDO-S101 combines the active structure of the alkylating agent bendamustine with that of the HDAC inhibitor vorinostat through fusion technology⁶. When used in malignant cells, alkylating agents have been shown to cause breaks in the tumour cell DNA that result in cell death⁸, while HDAC inhibition is known to suppress gene transcription and prevent the growth of cancer cells⁹. In addition, there is some evidence that HDAC inhibition may influence control mechanisms that protect against cell death⁹.

The parent molecules that constitute EDO-S101 are both well-established anticancer agents whose properties have been extensively studied^{8,9}. Bendamustine has been shown to regulate pathways for DNA repair and cell death, while vorinostat blocks cell cycle and division preventing further growth in a broad spectrum of cancer cells, with little toxicity to non-malignant cells^{8,9}. The rationale underlying the selection of these two agents as the component parts of EDO-S101 is that chromatin is the functional and structural unit of DNA, which is very tightly coiled in its normal state, but is relaxed by HDAC inhibition^{6,10}. Thus, it is anticipated that vorinostat may relax DNA within malignant cells, and so make it more accessible to the damaging effects of bendamustine⁶. Once bendamustine has produced damage to the DNA of the malignant cells, it is possible that

vorinostat may play an additional role by impairing the ability of the tumour cells to repair the resulting DNA damage⁶.

Initial preclinical investigations with EDO-S101 have successfully demonstrated that the full function of both parent molecules has been retained within the fusion molecule. Repair proteins have been shown to be less abundant following a strong DNA damage response and cell death was triggered at lower concentrations of the fusion molecule than with bendamustine alone⁶. The bi-functional activity displayed by EDO-S101 has been demonstrated to be superior, and more sustained, than the efficacy of either agent when given individually, or as combination therapy, thus exhibiting the synergy that occurs between the active structures of bendamustine and vorinostat when fused by the A-DAC principle to form EDO-S101^{6,11,12}. Furthermore, in myeloma cells isolated from patients, EDO-S101 was shown to overcome resistance to alkylators, such as melphalan, and increase the effect of agents such as dexamethasone, lenalidomide and proteasome inhibitors^{11,12}.

HDAC inhibitors are known to induce multidrug resistance which, to date, has contributed to a poor prognosis in cancer treatment¹³. The mechanism contributing to drug resistance is under investigation, particularly in haematological malignancies, however, the ability to instil non-resistant properties through a synergistic reaction would be of particular benefit^{14,15}.

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Pre-clinical data suggest that the A-DAC, EDO-S101 will demonstrate strong activity in haematological and solid malignancies⁷. This is currently being investigated in a first-in-human clinical study of EDO-S101 (NCT02576496) in patients with relapsed/refractory haematological malignancies¹⁶. This single-group, open-label study aims to investigate the safety, pharmacokinetic profiles and efficacy of EDO-S101¹⁶. The outcomes of this study are eagerly awaited, underpinning as they do the whole future development of fusion technology.

Fusion technology – beyond oncology

It is too early to fully speculate as to any potential role for fusion technology beyond the oncology arena. At the time of writing, the first-in-human study for EDO-S101 is recruiting, and although early indications are positive, it is impossible to definitively comment on the efficacy and tolerability of this fusion molecule. However, the common application of combination treatment regimens in oncology makes it the ideal arena for initial assessment of fusion technology, therefore, any future applications would, by definition, also target those diseases where combination treatment is currently considered to be the standard of care.

One area where the use of fusion technology might be considered in the future, is the treatment of autoimmune diseases. Indeed, some very early pre-clinical investigations were conducted into Lupus, Rheumatoid Arthritis (RA) and Multiple Sclerosis (MS).

While diseases such as RA might benefit from this approach, there are already a number of effective treatments available for these patients. However, there are other autoimmune diseases where options are more limited. For example, granulomatosis with polyangiitis (GPA), previously known as Wegener's granulomatosis (WG), is a systemic disorder that involves both granulomatosis and polyangiitis. It is a form of vasculitis that affects small- and medium-size vessels in many organs. The majority of patients with GPA experience disease flares after conventional medications are tapered, and at present there is no consistently safe, effective treatment for the maintenance of remission. Tumour necrosis factor α (TNF α) has been implicated in the pathogenesis of GPA, however, unlike other TNF α -mediated diseases, such as rheumatoid arthritis and psoriasis, anti-TNF α blockade has not been shown to provide effective management¹⁷. Given the correlation between improvements in disease and reduction in leukocyte transmigration observed in experimental models of glomerulonephritis and vasculitis,¹⁸ it is pos-

sible that a fusion molecule with bi-functional modality designed to target the key immune components of these diseases might prove beneficial.

The advantageous synergy observed in preclinical studies with EDO-S101 has demonstrated the possibility of a greater potential for previously well-characterised agents as fusion molecules. While oncology has been chosen as the testing ground for this new technology, offering as it does a continued level of unmet medical need, there are many therapeutic areas where optimal treatment is yet to be found. These are fascinating times as we begin to investigate the first example of fusion technology in human studies. As we learn more about EDO-S101 and understand the enhanced synergies of a fusion molecule, we will be better placed to identify those agents where fusion technology may confer a benefit. This, in turn, will enable us to fully consider the application of this new and innovative approach to future fusion molecules and therapy areas.

Fusion technology – the commercial imperative

At this time, it is difficult to fully assess the impact that fusion technology might have within the pharmaceutical marketplace. The obvious opportunities for these agents will be for the treatment of those diseases where there is currently an unmet medical need. This may encompass those diseases where short remissions are observed after treatment or the management of rare diseases, the treatment of which has been under-explored.

Within the oncology arena it is reasonable to speculate that, should the outcomes of clinical studies support preclinical findings, the hypothesis of fusing the active moieties of two anti-cancer treatments with disparate but complementary modes of action within a single molecule will be ground-breaking. An efficacious fusion molecule will facilitate the development of a new range of treatment options and may, in time, become standard of care. However, when considering the potential of fusion technology, it should be remembered that this is one more step in the continuing evolution of chemotherapy and we cannot yet fully speculate where this evolution may continue to progress. The preclinical findings for EDO-S101 have been extremely encouraging, and while it is not possible to state definitively which tumour types or patients may benefit most from this treatment approach until solid clinical trial data are available, what is clear is that this is an exciting era in oncology drug discovery and the future holds much promise.

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Summary and conclusion

Chemotherapy is becoming 'smarter' and continually evolving to meet the needs of oncology patients and fusion technology represents another step forward in this evolution. By fusing together the active structures from two established anti-cancer agents with disparate, but complementary, mechanisms of action, the intention is to enable these agents to act in synergy to improve outcomes for patients. EDO-S101 is the first example of the A-DAC principle, which fuses together an alkylating agent with a pan histone deacetylase (HDAC) inhibitor. EDO-S101 has shown much promise in preclinical studies, with synergistic activity greater than that of either of the parent molecules given as either monotherapy or in combination. This molecule is currently undergoing clinical assessment, and once the results of these studies are available it will be possible to fully determine the future potential of this treatment approach and the impact that it may have upon the lives of cancer patients. Once these data have been analysed, it will then also be possible to consider the future application of fusion technology for drug development in other diseases, principally autoimmune diseases. Furthermore, the positioning of fusion technology within the pharmaceutical marketplace should also become clear, and it will be possible to assess fully the unmet medical need in target disease areas and to speculate as to the possible market share that might be taken by fusion molecules. We live in an exciting time of drug discovery, chemotherapy has evolved considerably from the nitrogen mustards and it will be interesting to see how it continues to evolve into the future. **DDW**

Dr Thomas Mehrling is CEO of Mundipharma EDO GmbH, Basel. He brings extensive experience with more than 17 years in the industry to this role. During his career, he has held various senior positions in different companies across almost all functions in drug development and commercialisation. Most recently, he held the position of International Director Oncology Strategy (2011-13). From 2004 to 2011 he served as European Director Oncology at Mundipharma International Ltd. During his tenure the oncology business of the European Mundipharma network of independent associated companies was set up and two major products were launched in Europe, DepoCyte® and Levact® (Ribomustin®, Treanda®). He joined Mundipharma in 2000 as Head of Business Development. Prior to Mundipharma, he was Senior Vice-President of the global CRO Medical

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