Short communication

By looking back we can see the way forward: enhancing the gains achieved with antihormone therapy

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Sir Alexander Haddow discovered the first chemical therapy to treat cancer [1]. Based on Paul Ehrlich's pioneering work that resulted in chemical therapy or chemotherapy to treat bacterial infections [2], Haddow investigated the therapeutic potential of numerous polycyclic hydrocarbons to cause tumour regression in experimental animals. Some compounds were effective, but the fact that they were known carcinogens prohibited further exploration in humans. Nevertheless, the triphenylethylene-based oestrogens [3] have a structural similarity to polycyclic hydrocarbons and they were also observed to cause tumour regression in animals. This was the translational basis of Haddow's landmark clinical experiments to evaluate the efficacy of high-dose oestrogen on the growth of breast and prostate cancer. Responses were noted but Haddow later commented [4] in 1970 during the inaugural David A Karnofsky lecture that, 'The extraordinary extent of tumour regression observed in perhaps 1% of postmenopausal cases has always been regarded as of major theoretical importance and it is a matter of some disappointment that so much of the underlying mechanisms continue to elude us.'

High-dose oestrogen therapy was introduced into clinical care during the 1950s [5] for the treatment of postmenopausal women with metastatic breast cancer. This approach complemented the use of ovarian ablation (using radiation at that time) in premenopausal patients, but the observation that high-dose oestrogen was an effective treatment for one in three elderly postmenopausal breast cancer patients remained a mechanistic paradox until recently [6].

Through serendipity, a young endocrinologist, Leonard Lerner at Merrell Dowe Pharmaceuticals in the USA, recognized that a triphenylethanolic compound being tested as a cardiovascular drug had a structure similar to the triphenylethylenes [7]. He asked to test the compound but found that there was no oestrogenic activity in any species tested, only anti-oestrogen activity. The compound, MER25 or ethamoxytriphetol, was the first nonsteroidal anti-oestrogen [8]. However, it was the fact that nonsteroidal anti-oestrogens were postcoital antifertility agents in rats that drove the structural evolution of triphenylethylene-based oestrogens to become a whole range of novel anti-oestrogenic compounds [9]. Regrettably, the promise of preventing pregnancy was premature because the compounds actually induced ovulation [10]. Also, drug toxicities noted during the 1960s and 1970s retarded any serious consideration of the non-steroidal anti-oestrogens as therapeutic agents for indications such as breast cancer therapy [10]. Only ICI 46,474, the *trans* isomer of a substituted triphenylethylene [11], took a tenuous path to clinical testing in breast cancer [10,12] and was subsequently kept on life support to be reinvented [13] as a potential targeted therapy for the long-term adjuvant treatment and prevention for oestrogen receptor positive breast cancer.

Today, the advance with the clinical implementation of the scientific strategy is profound [14,15], and the practice of oncology has progressed significantly over the past three decades [6]. However, the consequences of long-term antihormonal therapy is drug resistance, and it is the laboratory study of the drug resistance of tamoxifen and subsequently the aromatase inhibitors that has provided the opportunity to solve the paradox of high-dose oestrogen therapy in breast cancer. Solving this mystery has had the potential to show the way forward for future advances in cancer care.

Models to study the development of drug resistance to long-term tamoxifen resistance were first reported 20 years ago [16,17]. Drug resistance to tamoxifen develops within about a year in MCF-7 breast cancer cells. Inoculated cells grow into transplantable tamoxifen-stimulated tumours in ovariectomized athymic mice [16], and drug resistance (subsequently also noted for raloxifene [18,19]) is consistent with clinical

VEGFR = vascular endothelial growth factor receptor.

experience. However, it should be stressed that tamoxifen-stimulated growth is a unique form of drug resistance. Tumours stop growing when tamoxifen is withdrawn, but oestrogen also stimulates tumours to grow. This is the scientific basis for the use of an aromatase inhibitor or fulvestrant, the pure anti-oestrogen, after the development of tamoxifen resistance [20]. However, the finding that tamoxifen resistance actually evolves into new phases [21] provided an experimental basis for solving the mystery of the mechanism of high-dose oestrogen therapy and an opportunity to enhance the effectiveness of antihormonal therapy in patients rendered refractory to multiple anti-oestrogenic treatments.

Tamoxifen-stimulated MCF-7 breast tumours can only be maintained as a model of human disease by serial transplantation into tamoxifen-treated athymic mice; no appropriate cellular model is available. However, the realization that the model does not replicate adjuvant treatment with tamoxifen (5 or more years) raised the question of what occurs under these clinical circumstances. The discovery that physiological oestrogen causes rapid tumour regression of long-term (5 plus years) tamoxifen-resistant MCF-7 tumours [22] and the subsequent finding that the oestrogen-stimulated regrowth of regressed tumour would again respond to the anti-oestrogen tamoxifen [23] indicated a new strategic approach to cancer care. Simply stated, for the first time there was a novel method for killing antihormone-resistant breast cancer cells and then effectively retreating with tamoxifen to maintain responding patients for longer periods. The development of mechanistic studies and the important observations that the principle of oestrogen-stimulated tumour cell regression and apoptosis also applied to oestrogen-deprived cells (aromatase inhibitor resistant) [24-26] enhanced the overall relevance of the observations and provided opportunities for further mechanism based clinical trials.

The important study conducted by Lønning and coworkers [27] provides the laboratory-to-clinic translation of the fact that high-dose oestrogen treatment can produce a response rate of up to 30% among patients who have been treated with exhaustive antihormone therapy. The question now being addressed in multiple clinical studies is whether low-dose oestrogen therapy will be as effective in treating patients with a sensitized breast tumour.

With the evolution of thinking about oestrogen action following Haddow's success with the first chemical therapy [1], it is reasonable to examine how we can improve the efficacy of long-term antihormonal therapy and the putative 30% response rate of low-dose oestrogen therapy in metastatic breast cancer. We are pursuing two paths. To improve long-term antihormone therapy, we are investigating the value of long-term vascular endothelial growth factor receptor (VEGFR)2 inhibitors [28] to block residual oestrogen or selective oestrogen receptor modulator induced VEGF secretion [29]. The recent report that VEGF creates drug resistance to tamoxifen [30] implies that dual long-term adjuvant treatment with tamoxifen and a VEFGR2 inhibitor will have potential clinical merit. However, the key to success, we believe, is the use of low-dose VEGFR2 inhibitor with the adjuvant antihormone to avoid toxicity during long-term therapy.

To improve the value of low-dose oestrogen therapy treatment after exhaustive antihormonal therapy, we believe that the real question is why do 70% of tumours in the clinic not respond to oestrogen induced apoptosis? We have developed cell lines that either respond rapidly or have a delayed response to oestrogen. Using this approach, we have examined the inhibitor of glutathione synthesis buthionine sulfoximine, which has previously been evaluated in the clinic to improve responses to chemotherapy [31]. In preliminary studies, buthionine sulfoximine dramatically enhanced the response of refractory antihormone resistant cells to the early apoptotic actions of oestrogen.

We suggest that there is now a clinical opportunity to use our proposed clinical trial [6,32] design that employs a yet to be determined 12-week course of low-dose oestradiol therapy to treat patients after exhaustive antihormonal therapy. A succession of combined antisurvival agents could potentially improve response rates to well above the 30% rate in metastatic breast cancer rendered refractory by exhaustive antihormonal therapy. The novel test platform is rapid and has tumour response as the end-point. We believe that new combinations of agents could subsequently be employed in much larger trials without oestrogen once its apoptotic efficacy is established.

In closing, it is gratifying that the story of oestrogen action through the oestrogen receptor has continued to offer surprises in each decade since Haddow's report in 1944 [1]. By looking back, we have been able to plan a way forward to benefit patients.

Competing interests

The authors declare that they have no competing interests.

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