Underwater treasures for cancer treatment

Janet Fricker, Freelance writer

A compound derived from the humble sea squirt (Fig. 1) has been shown to have potent anti-cancer properties and could also inhibit multidrug resistance, recent reports have shown. The results of three Phase I clinical trials[1–3] have revealed that ecteinascidin-743 (ET743) has broad activity against several tumour types. ET743 is the first DNA minor-groove-specific drug to demonstrate feasibility in clinical trials and, furthermore, is first new drug for 30 years to show potential for use against sarcomas.

Marine discovery

ET743 was isolated from the Caribbean marine tunicate *Ecteinascidia turbinata* by PharmaMar (Madrid, Spain), a biopharmaceutical company devoted to the discovery and development of novel anti-cancer drugs derived from marine organisms. The endogenous function of ET743 in sea squirts is thought to be as an anti-feedant or antimicrobial agent for protection in the natural environment. Although several of the compounds in *E. turbinata* exhibited antitumour activity, ET743 was selected for development on the basis of its anti-tumour activity and its abundance in the natural source.

Figure 1. The Caribbean marine tunicate *Ecteinascidia turbinata*, commonly known as the sea squirt, from which ecteinascidin-743 is derived.

Anti-cancer activity

When evaluated in the National Cancer Institute *in vitro* anti-cancer drug screen[4], low concentrations of ET743 caused 50% cell death in cancers of the colon and nervous system, as well as melanoma, renal and non-small-cell lung cancer. In addition, promising growth-inhibition was demonstrated against a variety of human tumour xenografts implanted in nude mice[5].

ET743 is a tetrahydroisoquinolone alkaloid that consists of three domains or 'rings' (Fig. 2). Its mechanism of action against tumours has yet to be fully elucidated; however, its cytotoxicity results primarily from the selective alkylation of the *N*-2 amino group of a guanine residue in the minor groove of DNA. Two of the rings make close contact with the double helix causing it to bend toward the major groove, whereas the third ring positions itself outside the complex and is exposed to the nuclear environment. 'The significance of the third ring sticking out is that it can act as a "fishing hook", interacting with proteins and interfering with DNA–protein associations, thereby anticipating activity in persistent tumours and giving us a rationale for combination therapy' says Jose Jimeno, Vice President of Clinical R&D at PharmaMar. In fact, it appears to hook, and thus inhibit, the multidrug resistance-1 gene product (MDR1), a transporter that is involved in the drug resistance frequently acquired by tumour cells. Further, a recent paper stated that ET743 inhibits the transcription of *MDR1* by multiple inducers without affecting constitutive *MDR1* transcription[6]. Other putative anti-cancer mechanisms of ET743 include its ability to block the cell cycle in late S and G2 phases, and to affect the organization and assembly of the cellular microtubule network, thus preventing cell division. Moreover, pharmacological concentrations of ET743 have been shown to block cellular transcription in a promoter-specific manner[7].

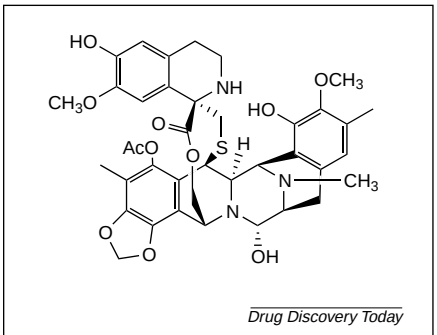

Figure 2. Structure of ecteinascidin-743.

Clinical trials

In Phase I studies to define the maximum tolerated dose and the Phase II tolerated dose, ET743 was given as a 24 h continuous infusion every three weeks to 52 patients with treatment-refractory solid tumours. The study established a maximum tolerated dose of 1.8 mg per

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m^2, and a recommended dose for low-risk patients of 1.5 mg per m^2, administered every 21 days[1].

The principal dose-limiting toxicities observed in these studies were neutropenia, thrombocytopenia and fatigue. In addition, grade 3–4 elevations in serum transaminase levels occurred in 48–69% of the patients treated at the recommended Phase II doses, but were not considered to be dose-limiting because the observed hepatotoxicity was reversible and non-cumulative, even after multiple courses of treatment. 'Of significance, were the observations that there was no hair-loss, mucositis, diarrhoea or cardiac toxicity, which should improve the quality of life for patients,' says Jimeno.

A second Phase I study involved the administration of ET743 as a continuous intravenous infusion over 72 h, every 21 days, in 21 adults with refractory solid tumours. This was significant, because earlier work in human tumour cell lines had shown that the drug was more toxic when continuous exposure was extended from 24 h to three days. It was found that the increased duration resulted in decreased myelosuppression and comparable hepatotoxicity[2].

There is growing evidence that ET743 could be particularly helpful in adult soft-tissue sarcomas. Currently, more than 50% of all patients with this cancer die within five years of the primary diagnosis as a result of widespread metastatic disease. In a Phase I study of 29 patients, ET743 showed anti-cancer activity in advanced, highly pretreated sarcoma patients and also against osteosarcoma[3]. The results of three pivotal Phase II trials including a total of 192 patients with resistant sarcoma are due to be presented at the American Society of Clinical Oncology meeting (San Francisco, CA, USA, 12–15 May, 2001), and are expected to confirm the therapeutic role of ET743 in adult patients bearing resistant relapse to conventional therapies, suggesting an improvement in survival rates. Furthermore, a Phase III trial of ET743 in sarcomas is currently under implementation in the USA.

Phase II trials to evaluate the efficacy of ET743 against different types of tumours including ovarian, melanoma, colon, lung and breast are now in progress, as well as a Phase I paediatric trial of solid tumours that are resistant to standard therapies. 'One exciting possibility for ET743 is that it could be combined with other cancer drugs to produce a synergistic effect. It could, in theory, prevent their problems with drug resistance,' says Jimeno. To this end, a Phase I trial combining ET743 and doxorubicin, and additional Phase I studies combining ET743 with platin compounds and taxanes are underway.

References

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Dr Joanna Owens, *Drug Discovery Today*, 84 Theobald's Road, London, UK WC1X 8RR.
tel: +44 (0)20 7611 4365, fax: +44 (0)20 7611 4485
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