Eribulin: Rediscovering Tubulin as an Anticancer Target

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Abstract
Eribulin mesylate (E7389) is a synthetic analog of the marine macroclide halichondrin B, which acts as a novel microtubule modulator with a distinct mechanism of action. Two eribulin mesylate phase 1 studies exploring weekly and 3-weekly schedules are reported in this issue. These trials show linear pharmacokinetics, a toxicity profile consisting in neutropenia and fatigue, and early hints of antimutator activity. In this commentary we give a brief historical perspective of the halichondrins and put into context eribulin mesylate as a novel tubulin modulator.

From the Sea to the Clinic: from Halichondrin B to Eribulin Mesylate

Eribulin mesylate (E7389, Eisai Research Institute, Andover, MA) is a microtubule dynamics inhibitor that is a simplified, synthetic analog of the marine natural macroclide halichondrin B, which was first isolated from the Japanese sponge Halichondria okadai (1), and subsequently from several unrelated sponges belonging to the Axinella family (2). Initial investigations into the bioactivity of halichondrin B revealed that it bound tubulin at a site close to the vinca site altering depolymerization (3), with no effect on colchicine binding (4). Halichondrin B inhibited the formation of an intra-chain cross-link between two sulphhydryl groups in beta-tubulin, it had no effect on alkylation of tubulin sulphhydryl groups by iodoacetamide (unlike vinblastin), and enhanced the exposure of hydrophobic areas on the tubulin molecule. At therapeutic concentrations conventional tubulin modulators such as taxanes, epothilones, and vinca alkaloids inhibit both growth and shortening of microtubules. The unique mechanism of action of the halichondrins secondary to a specific conformational effect suppresses microtubule growth with no effect on microtubule shortening, and also sequesters tubulin into nonfunctional aggregates (5).

Early experiments showed anticancer activity (1), but further work was limited by availability of the natural product. The National Cancer Institute (NCI) provided funds to trawl-harvest 1 metric ton of the deepwater sponge that yielded 310 mg of halichondrin B to continue development. At approximately the same time, a synthetic chemistry laboratory succeeded in the total synthesis of halichondrin B in 90 chemical steps (6). This synthetic work was expanded by scientists at the Eisai Research Institute who produced a range of halichondrin B variants that remained bioactive while being structurally more stable than their natural counterparts (7). Of those analogs, eribulin mesylate (E7389) had activity in preclinical models of diseases in which microtubule inhibitors already have a therapeutic role such as breast or ovarian cancer, but also in other diseases in which they are less relevant such as colorectal cancer. This issue of Clinical Cancer Research reports two phase 1 studies that evaluated eribulin mesylate in patients with solid tumors.

Phase 1 Clinical Trial Results
The studies by Goel and colleagues (8) and Tan and colleagues (9) investigated the maximum tolerated dose, toxicity profile, preliminary anticancer activity, and pharmacokinetics of a 1-hour infusion of eribulin mesylate administered on days 1, 8, and 15 of a 28-day cycle, and on day 1 of a 21-day cycle (referred further as weekly and 3-weekly schedules for clarity), respectively. In the weekly study 32 patients received doses from 0.25 to 1.4 mg/m², with dose-limiting toxicity (DLT) consisting of neutropenia in two patients (one with associated grade 3 fatigue) at the higher dose. Thus, the maximum tolerated dose (MTD) was 1 mg/m², a dose in which only one of six evaluable patients had DLT. In the 3-weekly study 21 patients received doses from 0.25 to 4 mg/m², with DLT consisting of neutropenia in all three patients treated at 4 mg/m², and in two of three patients at 2.8 mg/m². The MTD was 2 mg/m², a dose level at which only one of six evaluable patients had DLT. Both trials followed an accelerated titration escalation strategy allowing one patient per cohort per site. The accelerated titration design allowed rapid escalation of the dose and the one (or two) patient cohort strategy was accurate in the weekly schedule; however two dose levels had to be de-escalated in the 3-weekly schedule because of reversible toxicity.

In both studies the predominant toxicities were neutropenia and fatigue. The 3-weekly schedule had an earlier onset of neutropenia with multiple febrile neutropenia occurrences as early as day 7 of the first cycle, and showed a significant incidence of alopecia. Neurotoxicity was reported in eight and one patients in the weekly and 3-weekly studies, respectively.
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Eribulin is prepared as an aqueous solution with no solvent needs. Linear pharmacokinetics were documented in the studied range, with rapid distribution, slow elimination, and low renal excretion of unchanged drug. The weekly schedule provides slightly higher drug exposure to plasma levels above 2 ng/mL after each infusion, which approximates the IC50 (2 nM) of many of the studied cell lines.

Perspective

Eribulin mesylate is a microtubule dynamics modulator with a novel mechanism of action. Exploring both weekly and 3-weekly schedules is a pragmatic strategy in view of the schedule-dependent efficacy discrepancies of paclitaxel and docetaxel that seem more active in weekly and 3-weekly regimens, respectively (10, 11). The higher peak drug concentrations achieved in the 3-weekly eribulin regimen may explain the earlier and more profound neutropenia, similar to docetaxel (12). On the other hand the weekly schedule hinted a higher incidence of neurotoxicity, similar to paclitaxel (10).

High toxicity (13, 14) and somewhat slower than expected efficacy (14–17) of targeted therapy combinations in unselected populations argue in favor to continue developing chemotherapy-containing regimens. Tubulin polymerization (vinca alkaloids) or depolymerization (taxanes) inhibitors have a prominent role in the treatment of cancer, and the recent success of ixabepilone (18) showcases that continued exploitation of this target is warranted. If modulating the same αβ-tubulin heterodimer subunit as the taxanes still results in substantial efficacy in taxane-refractory patients, exploring a different mechanism of action could provide an additional advantage.

A large (n = 103) phase 2 study of eribulin using a bolus weekly schedule (19) in heavily pretreated breast cancer patients was recently reported (20). Eribulin mesylate at a dose of 1.4 mg/m² was initially given by a 2 to 5 minute infusion on days 1, 8, and 15 of a 28-day cycle; frequent day 15 neutropenia prompted exploring an alternative regimen of days 1 and 8 of a 21-day cycle. The independently reviewed objective response rate was 12%. Toxicities in this broader population were similar (four median number of prior therapies), and the response rate was 12% in both studies.

This work highlights the relevance of exploring alternative, natural backbones for new drug development. This is supported by evidence suggesting that by mimicking properties of natural compounds, combinatorial products might be made that are substantially more diverse and have greater biological relevance (22). The sea is a relatively unexplored but validated source of such structures (23), dating back to the development by Bergmann and colleagues of ara-A (vidarabine) and ara-C (cytarabine) based on unusual arabino- and ribo-pentosyl nucleosides from sponges collected in Florida (24). In 2004 ziconotide (α-conotoxin MVIIA), a synthetic equivalent of a peptide from the fish-hunting snail Conus magnus, was approved for severe chronic pain in spinal cord injury (25). Trabectedin (ET-743), an extract from the Caribbean tunicate Ecteinascidia turbinata received Orphan Drug designation from American and European regulatory authorities for soft tissue sarcomas and ovarian cancer, and is registered since 2007 in Europe for the treatment of soft tissue sarcomas. There have been however a significant number of marine compounds (particularly antimitotics) whose clinical programs have been less successful, such as the cryptophycins, (+)-discodermolide, and the hemiererylins (23). Compound supply has been limited in many such initiatives despite highly ingenious solutions, including advanced aquaculture and semisynthetic methodologies.

Eribulin mesylate’s development was facilitated by a partnership between academic and industry scientists that resulted in the identification of a synthetic halichondrin allowing scaled-up production and the conduction of clinical trials including the two studies subject of this commentary. These lean and well-executed trials show linear pharmacokinetics and consistent toxicity results, notably the dose ratio between the weekly and 3-weekly schedules is identical to that of similar taxane regimens. After adapting the weekly schedule owing to feasibility concerns in heavily pretreated populations, eribulin showed single-agent efficacy in taxane-refractory breast cancer patients comparable to that of recently approved tubulin inhibitors; results from phase 3 studies are eagerly awaited. Eribulin’s ongoing development plan includes single-agent studies in ovarian, prostate, urothelial, and non-small cell lung cancers, and combinations with gemcitabine and cisplatin.1

Finally, an opportunity lies in the early identification of determinants of activity to enrich trials and individualize therapy. Markers for tubulin modulator efficacy prediction such as tubulin (26) and microtubulo-associated protein tau (27) expression have been proposed and need to be explored while developing established and novel (28) tubulin inhibitors. In earlier work with eribulin a correlation was sought between its efficacy in breast cancer models and expression of the seven human β-tubulin isotypes (I, II, III, IVa, IVb, V, and VI), showing a positive association between βIII tubulin and sensitivity to eribulin (29). If successful these exciting studies will take us a step closer to the realization of truly individualized anticancer therapy.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

1 http://clinicaltrials.gov
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References

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