

Eribulin drug review

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Abstract

Eribulin is an anticancer drug approved for treatment of metastatic breast cancer. This drug is a synthetic derivative from Japanese marine sponge *Halichondria okadai*. It acts by interfering with the microtubular growth ultimately leading to apoptosis after prolonged mitotic blockage. In patients with metastatic breast cancer refractory to anthracyclines and taxanes, eribulin is one of the life-saving options. Neutropenia, neuropathy and QT prolongation are the most frequent adverse events associated with this drug. Phase I/II trials are also underway in refractory lung, ovarian, pancreatic, bladder, and soft tissue tumors. Larger prospective studies will define the role of this drug in a wide variety of tumors, and the future looks very promising.

Key words: Eribulin, taxane, breast chemotherapy

Introduction

Eribulin is an anticancer drug which can be used in the treatment of breast cancer and is now finding its way in the treatment of other solid malignancies. It is derived from a natural product and exerts its action by altering the dynamics of the microtubules. We present a comprehensive review of this promising drug with regards to its mechanism of action, uses, toxicity profile, and clinical trials.

History

Eribulin mesylate (E7389) was developed by the Eisai Research Institute. In 1985, Hirata and Uemura,^[1] originally isolated halichondrin B from the natural Japanese marine sponge *Halichondria okadai* and subsequently from other sponges from the *Axinella*, *Phakellia* and *Lissodendoryx* families.^[2] Though the molecule had strong anticancer activity, its procurement from the sea was difficult and the National Cancer Institute funded the harvesting of these marine sponges for research. The breakthrough happened in 1998 when a synthetic analogue was prepared by Dr. Yoshito Kishi of Harvard, who developed a completely synthetic halichondrin B. Subsequently, the synthetic technology was licensed from Harvard to Eisai Research Institute who accomplished the synthesis of the resulting drug, E7389 (NSC 707389) with similar anticancer activity but more stability.^[2] The drug was approved within 8 months of its application. It was approved by the US Food and Drug Administration (FDA) on November 15, 2010 for the treatment of metastatic breast cancer.^[3] The approval was based on the dramatic results of the landmark

EMBRACE trial (Eisai metastatic breast cancer study assessing physician's choice versus eribulin). Eribulin is now approved in 40 countries worldwide.

Molecule

Eribulin mesylate is a synthetic analogue of halichondrin B which is a large polyether macrolide derived from a very strong natural mitotic tubule inhibitor. It has a molecular weight of 826.0 (729.9 for free base). The empirical formula is C₄₀H₅₉NO₁₁•CH₄O₃S. It is a clear, colorless solution.

Mechanism of Action

Eribulin acts by inhibiting the dynamics of the microtubules. It binds to the plus ends of the microtubules and suppresses the microtubule growth in the interphase cells without affecting the shortening phase and sequesters tubulin into nonproductive aggregates, leading to G₂/M cell-cycle block and ultimately apoptosis after prolonged mitotic blockage.^[4] Its mechanism is distinct from other microtubule inhibitors like vinca alkaloids and taxanes, which affect both the shortening and growing phases. While vinca alkaloids bind at both the ends (alfa and beta), taxanes and epithilones bind at the beta end and specifically on the inner aspect of the microtubule. Another distinctive feature is that eribulin binds either at the interface between the alfa and beta subunits of the microtubule or at the beta subunit alone and is hence now being studied extensively in the treatment of patients with taxane-resistant breast cancer arising due to beta tubulin mutations.

Pharmacodynamics/Pharmacokinetics

It has linear pharmacokinetics with a t-half of 40 h and is around 49%-65% protein bound. The drug gets rapidly distributed but slowly eliminated. Majority of the drug is eliminated through the bile and excreted unchanged in the faeces.

Dosing

Eribulin mesylate is manufactured as a 5 mg vial and the drug concentration is 0.5 mg/mL. No routine premedication is needed. It has to be administered as 1.4 mg/m² over 2-5 min on days 1 and 8 of a 21 day cycle, either undiluted or diluted in 100 mL 0.9% normal saline.

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Review of Clinical Trials

1. In a phase 1 trial, the maximum tolerated dose, dose limiting toxicities, and pharmacokinetics of eribulin were studied in patients with advanced solid tumors. It was concluded that at a dose of 2 mg/m² administered over a period of 1 h, eribulin had a manageable toxicity profile and dose escalation was associated with increased neutropenia.^[5]
2. Based on its mechanism of action on microtubules and activity in breast cancer cell lines it was hypothesized that this drug may have action in refractory breast cancer.^[6] In a Japanese phase 2 study, eribulin was used in heavily pretreated metastatic breast cancer patients. The end point of the study was overall response rate (ORR) which was 21.3%, with a progression-free survival (PFS) of 3.7 months and overall survival (OS) of 11.1 months.^[7]
3. In a single arm, open labeled, phase 2 study by Cortes *et al.*,^[8] eribulin was used in locally advanced and metastatic breast cancer patients previously treated with an anthracycline, taxane, and capecitabine. The investigator reported ORR was 14.1%, with a median duration of response of 4.1 months, PFS of 2.6 months, and OS of 10.4 months. Neutropenia was seen in 54%, fatigue in 10%, and peripheral neuropathy in 6.9% patients
4. In a phase 2 study by Linda *et al.*,^[9] eribulin was studied in breast cancer patients who were previously treated with an anthracycline and taxane, and found an OS of 9 months with a similar toxicity pattern of neutropenia and neuropathy
5. In the landmark EMBRACE trial, 762 women were randomly allocated to receive either eribulin or any other monotherapy as per the treating physician's choice. Patients in the eribulin arm had an OS of 13.1 months compared with 10.6 months in the control arm.^[10]

Indications

As monotherapy for the treatment of late stage or metastatic breast cancer in patients who have previously received at least two chemotherapy regimens, including an anthracycline and taxane. This has been approved by the US FDA on November 15th 2010. The options in patients with anthracycline and taxane resistant breast cancer include capecitabine, gemcitabine, vinorelbine, and Ixabepilone. Eribulin which was released in India this year, with the cost of Rs. 4.8 lakh per four cycles is far more costly than other available options. Having poor cost-effectiveness this drug was rejected by NICE. The NICE committee also noted that the mean overall survival gain was 2.7 months from the overall intention to treat population, and further concluded that eribulin could not be considered as a cost-effective use of resources for National Health Service use even if all of the criteria for being a life-extending, end-of-life treatment were met.^[11] However, a ray of hope is that the manufacturer has initiated a patient support program to

make this drug available to the underprivileged patients in India at significantly reduced or no cost.

Toxicity

- Neutropenia-the incidence of > grade 3 toxicity is around 57%. Patients with transaminitis >3ULN have higher incidence of neutropenia. The incidence of febrile neutropenia is around 5%. Mean time to nadir was 13 days with a mean time to neutrophil recovery of 8 days. Thrombocytopenia (> Grade 3) occurs in 1% and grade 3 anemia in 2% patients. In the phase 3 study G-CSF requirement was around 18%; however, prophylactic usage is not recommended
- Peripheral neuropathy-Incidence is around 8% for grade III neuropathy and 0.4% for grade IV neuropathy. Both sensory and motor neuropathy was seen. Nearly 1/5th of neuropathy do not recover. The mechanism of peripheral neuropathy is in other taxanes is not clear; however, it is presumed to be more of an axonal neuropathy affecting the transport system in the axons. Studies in mice comparing neuropathies of eribulin, paclitaxel, and ixabepilone have shown that at equivalent doses, eribulin induces less neuropathy.^[12] Prior to each dose of eribulin peripheral neuropathy has to be assessed and if needed dose has to be modified accordingly as mentioned below (nonhematological toxicity)
- Teratogenic based on animal models, however, studies in human being are lacking. In pregnant rats, it produced increased abortions, reduced fetal weight with soft tissue malformations including absence of lower jaw, tongue, stomach, and spleen
- QT prolongation is commonly observed on day 8, independent of eribulin concentration, with no QT prolongation on day 1. The maximum mean QTc change from baseline on day 8 was 11.4ms on day 83. Electrocardiogram monitoring is required only when eribulin is planned in patients with congestive cardiac failure, dysrhythmia, dyselectrolyemia, and concurrent use of drugs which cause QT prolongation. Serum potassium and magnesium levels should be monitored frequently
- Has low emetic risk and no routine premedication is indicated
- Has low allergic risk, as there are no solvents like cremophor or polysorbate 80. No premedications required, no premixing required as it is prepared as an aqueous solution
- Other side effects which are usually mild include all grades of alopecia (in 40%-50%), fatigue (all grades 54% and grade 3 in 8%), constipation (all grades in 25%), myalgia (all grades in 22%), and all grades of respiratory complaints like cough and dyspnea in around 16%.

Dose modifications

- For Child Pugh A and B hepatic impairment, the dose should be reduced to 1.1 and 0.7 mg/m² respectively. Child-Pugh score is based on five parameters with each given 1-3 points (bilirubin <2, 2-3,>3 serum

albumin >3.5, 2.8-3.5, <2.8, PT INR <1.7, 1.7-2.3, >2.3, ascites-none, mild, moderate to severe and hepatic encephalopathy none, grades I-II, grades II-IV)

- If creatinine clearance is 30-50 mL/min, the dose should be reduced to 1.1 mg/m²
- If grade 3 or 4 toxicities do not resolve by day 15, then day 8 dose has to be omitted. If it decreases to < grade 2, then it can be given at reduced dose to 1.1 mg/m² and the next cycle should be given after 2 weeks. The dose has to be permanently reduced from 1.4 to 1.1 mg/m² if any of the following occur:
 - a. ANC <500/mm³ for >7 days
 - b. ANC <1000/mm³ with fever or infection
 - c. Platelets <25,000 or <50,000/mm³ requiring transfusion
 - d. grade 3 or 4 nonhematological toxicity
 - e. If the dose was reduced to 1.1 mg/m² or omitted in the previous cycle due to toxicity
- If the patient develops recurrence of the above said toxicity (hematological as mentioned above/grade 3 or 4 nonhematological) at 1.1 mg/m², then the dose has to be reduced to 0.7mg/m². If the patient develops the same toxicity at 0.7 mg/m², then the drug has to be discontinued.

Precautions

1. It should not be mixed with dextrose containing solutions as it is incompatible
2. To be avoided if absolute neutrophil count <1000/mm³, platelets <75,000/mm³, grade 3 or 4 non hematological toxicity licensing details:^[13] It is marketed under the trade name HALAVEN (eribulin mesylate). It is available as an intravenous preparation as 1 mg per 2 mL (0.5 mg/mL). It is approved by the US FDA and marketed by Eisai Co under the trade name HALAVEN.

Off-label/experimental uses with ongoing trials

Eribulin is now being studied in the treatment of other advanced solid malignancies. Most studies are phase I-II trials. A study is being conducted in Japan in which eribulin is used in the treatment of advanced soft tissue sarcoma not amenable to surgery or radiotherapy. It is also being studied in nonsmall cell lung cancer patients who have progressed during or following platinum containing doublet chemotherapy and in prostate cancer patients who have not responded to hormone therapy. Other solid tumors where eribulin is being studied includes pancreatic, colorectal and bladder cancers. In breast cancer, it is also being tried as neo adjuvant chemotherapy in Her2 nonoverexpressing tumors.

Conclusion

Eribulin is an anticancer drug approved for treatment of metastatic breast cancer refractory to anthracyclins and taxanes. Derived from Japanese marine sponge, it acts by interfering with the microtubular growth. Neutropenia, neuropathy, and QT prolongation are the most frequent adverse events associated with this drug. With low

incidence of hypersensitivity, easy administration and being useful even in taxane resistant cases, this is a valuable drug in the oncologist's armamentarium against cancer.

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