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Eribulin and its application as anti-cancer treatment

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Abstract. Eribulin (E7389) is a synthetic small molecule medication with high anti-cancer efficacy exhibited in preclinical studies. It is a structure-simplified macrocyclic ketone analog of Halichondrin B, which can inhibit the development of microtubule that is essential for the mitosis of cancer cells. The U.S. Food and Drug Administration (FDA) has given eribulin approval as a third-line chemotherapy for patients with metastatic breast cancer (approved in 2010) or metastatic liposarcoma (approved in 2016). In a number of clinical trials, eribulin has shown outstanding efficacy and safety in the treatment of solid tumors, particularly for breast cancer and sarcoma. Current eribulin clinical trials focus on its use in the therapy of other various cancer types, including non-small cell lung cancer (NSCLC), salivary gland cancer, cervical cancer, urethral cancer, and prostate cancer, and its application in combination treatment. The present study summarizes the mechanism, development, and future directions of eribulin, with an emphasis on the results of clinical trials.

Keywords: eribulin, microtubule inhibitor, breast cancer, liposarcoma.

1. Introduction

Eribulin is a member of macrocyclic ketone derivatives currently applied as a small-molecule anti-cancer drug for cancer treatment, particularly for varied types of the soft-tissue sarcoma and breast cancer, as a result of its potent anti-mitotic activity through the suppression of microtubule dynamics. In 2010, the U.S. FDA initially approved eribulin as a chemotherapy drug for metastatic breast cancer, which offers an alternative treatment for patients who have received no less than two chemotherapy regimens containing taxane and anthracycline. In January 2016, FDA approved eribulin for the third-line chemotherapy of metastatic liposarcoma as single-agent therapy following the previous anthracycline-based treatment.

1.1. Development of eribulin

The inspiration for eribulin is from Halichondrin B (HB), a member of marine natural products, which has been reported to exhibit astonishing anti-cancer activity in murine and human tumor models [1,2]. However, the difficulty in extracting and chemically synthesizing HB due to its complex molecular structure limits its potential in novel anti-cancer drug development. A series of structurally simplified analogs of HB that retain the macrocyclic ketone moiety were synthesized and evaluated, in light of the additional analysis of the structure-activity relationship of HB that shows the anti-cancer activity is relevant to the macrocyclic ketone part corresponding to the right half of the molecule[3]. Eribulin initially named ER-086526 or E7389, represented highly potent *in vitro* and *in vivo* anti-proliferative

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activity within the same order of magnitude as HB among more than 180 candidates, which promoted the succeeding development of preclinical research and clinical trials.

Despite the chemical structure being simplified, eribulin remains one of the most complex small molecule drugs. The construction of the macrocyclic scaffold relies on the Nozaki-Hiyama-Kishi reaction (NHK reaction), which completes the crucial coupling of the two previously synthesized C1-C13 and C14-C35 segments, in the current production of eribulin for commercial use[4].

1.2. The mechanism of eribulin

Eribulin can block the mitotic process by preventing the development of microtubules, which are essential for spindle formation and function[5]. The drug molecule can bind to a single site of β-tubulin through hydrogen bonds and hydrophobic interactions with a similar but stronger affinity than HB, forming an eribulin-αβ-tubulin heterodimer and inhibiting polymerization[6]. This inhibits the development of microtubules by reducing free hydrophilic tubulin and dampening the dynamic balance between the polymerization and the depolymerization of microtubules. [7]. Eribulin's effect on microtubule dynamics can induce the break in the assembly of spindle organization and thus the blockage of the mitotic process at the G_2/M phase. This halted cell cycle progression results in continued inactivation of Bcl-2, which eventually prompts cancer cells to go through apoptosis[8]. Additionally, eribulin maintains its potency against tumor cell lines with paclitaxel resistance due to β-tubulin mutations with a unique tubulin interaction[9].

2. Clinical trials

2.1. Phase I trials

There is already more than 30 phase I studies of eribulin against advanced solid tumors that have been published, three earliest of which were the dose-finding studies. In the earliest phase I study, published by Synold et al., Eribulin was administered as a bolus once a week, three weeks out of four, to 40 patients with advanced solid tumors[10]. To determine the maximum tolerated dose (MTD), the administration was started at a dose of 0.125mg/m^2/wk and continued on a standard 3 × 3 dose escalation strategy. It was noted that few patients had dose-limiting toxicities (DLT) when the dosage level was increased to 2.0 mg/m^2/wk, including grade 3 febrile neutropenia and grade 4 neutropenia. Thus the MTD was found to be 1.4mg/m^2/wk. Another dose-finding trial was also reported by Synold et al., in which 21 advanced solid tumors patients were given eribulin intravenously at increasing doses of 0.25, 0.35, 0.5, 0.7, 1.4, 2, 2.8, 4, 5.6, and 8 mg/m^2[11]. The predominant DLT identified when the dosage was raised to 4 mg/m^2 was febrile neutropenia, which led to the conclusion that the MTD in this trial was 2 mg/m^2. The MTD of eribulin in the third phase I study was determined to be 1 mg/m^2 when eribulin was administrated as an intravenous injection (i.v) during an hour once a week 3 weeks out of 4[12]. The most prevalent adverse effects (AEs) in these trials, which were thought to be typical toxicities of taxanes, included neutropenia, alopecia, and fatigue[13]. Furthermore, eribulin was demonstrated to remain effective for taxane-resistant patients in these phase I trials, since the patients who had taken previous taxane-based chemotherapy experienced stable disease as well,

Several drug combination trials of eribulin have been reported. The dose-determining study of gemcitabine and eribulin for late-stage solid tumors demonstrated the viability and manageable safety profile of the combination of eribulin (1.0mg/m^2) and gemcitabine (1000mg/m^2) administered weekly 2 weeks out of 3[14]. Alterations in the biochemical liver enzymes, myelosuppression, and weariness were the most common adverse reactions. In another dose-escalation study of eribulin in combination with sorafenib, the recommended phase 2 dose (RP2D) in the treatment of solid tumors patients was found to be sorafenib 400mg twice daily in combination with eribulin as an intravenous infusion once a week 2 weeks out of 3 at a dosage level of 1.4 mg/m^2[15]. The adverse effects were analogous to those in monotherapy trials.

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2.2. Phase II trials

To date, more than 50 phase II trials have been finished, including the investigation into the eribulin-based chemotherapy of breast cancer, sarcoma, and other solid tumors.

In 2009 Vahdat et al. reported an open-label, single-arm, phase II study, in which 70 metastatic breast cancer (MBC) patients who had previously taken anthracycline-based and taxane-base chemotherapy were initially treated with eribulin as a weekly intravenous injection during 2 to 5 minutes 3 week out of 4, starting with a dosage level of 1.4 mg/m^2[16]. Owing to neutropenia observed in patients in the third week, the treatment plan was then modified and 33 patients in the second group were given eribulin once a week 2 weeks out of 3. Among the 87 assessable patients, the objective response rate (ORR), the primary endpoint, was found to be 11.5%, and the median overall survival (mOS) was found to be 9.0 months. The main AEs were consistent with those in several phase I trials, including neutropenic, fatigue, leukopenia, anemia, and nausea. In Another multicenter, open-label, single-arm, phase II trial, 299 adult female locally late-stage breast cancer or MBC patients, who had been given four treatments including anthracycline-based, taxane-based, and Capecitabine-based chemotherapy, were treated with eribulin once a week 2 week out of 3. Results showed an ORR (the primary endpoint) of 9.3%, and a clinical benefit rate of 17.1%, validating that eribulin remains efficacy in the treatment of taxane-resistant patients[17].

Schöffski et al. published the phase II study on different subtypes of soft-tissue sarcoma, in which eribulin was treated as a 2- to 5-minute weekly intravenous injection 2 weeks out of 3 at a dose level of 1.4mg/m^2[18]. Approximately half of the assessable sarcoma patients exhibited clinical benefit. In another open-label, nonrandomized trial in patients with liposarcoma, leiomyosarcoma, or other subtypes, the progression-free rate at 12 weeks (PFR_{12wks}) was determined to be the primary endpoint[19]. The PFR_{12wks} was found to be 60% and 31%, respectively, in patients with leiomyosarcoma/liposarcoma and other types, with 51% in total. The overall mPFS and mOS were 4.1 months and 13.2 months, respectively. These findings indicate the clinical effectiveness of eribulin for metastatic or advanced soft tissue sarcoma patients who had taken prior chemotherapeutic treatment, with a tolerable safety profile demonstrated by comparable adverse events (AEs) during the course of the treatment.

Phase II studies on several other tumors have been finished and published as well, including NSCLC, children's recurrent or refractory osteosarcoma, metastatic hormone-refractory prostate cancer, and recurrent or metastatic salivary gland maliganacies[20–23]. The efficacy and tolerability of eribulin in combination with other drugs were evaluated in a number of phase II trials. These trials included the application of eribulin combined with capecitabine, ixabepilone, ramucirumab, and Olaparib tablet in the therapy of varied classes of breast cancer[24–26].

2.3. Phase III trials

Currently, there are 11 completed phase III studies have been published, with MBC being the main disease. The efficiency and tolerability of eribulin against breast cancer were examined in the first two phase III trials, which were randomized, open-label, two-parallel-arm studies. One trial (Study 305) compared eribulin to Treatment of the Doctor's Choice (TPC), and 762 adult female locally late-stage or MBC patients who had previously undergone two chemotherapeutic medications or more, involving anthracycline- and taxane-based treatment, were enrolled[27]. Of these, 508 of these patients were assigned at random to receive eribulin treatment (1.4 mg/m2, once a week 2 weeks out of 3), and 254 received drugs of TPC. Among 247 patients in the TPC group, 61 patients received vinorelbine, 46 received gemcitabine, 44 received capecitabine, 38 received taxanes, 24 received anthracyclines, 2 received other chemotherapies, and 9 received hormonal therapy, with the exception of 6 patients who discontinued treatment and 1 who was moved to the eribulin group. The OS was the primary outcome measure. Results revealed a significant increase in the survival time, as the median OS times for patients treated with TPC and eribulin were 10.6 months and 13.1 months, respectively. The objective response rates (ORRs) of the eribulin group and TPC group, which served as the secondary endpoint, were 12% and 5%, respectively. 1102 adult females with MBC who had undergone up to three prior

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courses of chemotherapeutic treatment, including an anthracycline-based and a taxane-base therapeutic regimen were registered in another phase III study (Study 301) that examined the effectiveness of eribulin versus capecitabine for the treatment of metastatic breast cancer and locally advanced breast cancer[28]. Of the participants, 554 received eribulin (same administration), and 548 received capecitabine (1.25g/m^2, b.i.d., once a day for 2 weeks out of a 3-week cycle). The primary endpoints were PFS and OS. The results of study 301, in contrast to Study 305, revealed no obvious variances in median OS times (14.5 months for capecitabine versus 15.9 months for eribulin) and median PFS (4.2 for capecitabine versus 4.1 months for eribulin), demonstrating that eribulin and capecitabine have comparable efficacy. Further analysis of these two studies revealed that the eribulin treatment rather than TPC or capecitabine tended to improve the OS of patients with three or fewer previous regimens for breast cancer[29]. The safety profile for studies 305 and 301 was manageable. Leukopenia, peripheral neuropathy, and alopecia were observed to be the most frequently side effects, and neither trial reported any cases of treatment-related fatalities. These results suggested manageable, predictable, and clinically acceptable adverse effects profiles of eribulin.

Demetri et al. reported a randomized, phase III, multicenter, open-label trials in the therapy of late-stage leiomyosarcoma (LMS) and liposarcoma (LPS)[30]. 452 advanced LMS or LPS adult patients who had taken more than 2 prior chemotherapy treatments involving an anthracycline-base regimen were enrolled and were allocated to the eribulin group (228 patients) and dacarbazine group (224 patients) at random. The primary and secondary endpoints were OS and PFS. Results showed that the eribulin group exhibited higher median OS times compared with the control group (15.6 months versus 8.4 months). The secondary endpoint of PFS was improved as well. Patients in the dacarbazine and eribulin groups had median PFS times of 1.7 months and 2.9 months, respectively. These results suggested that eribulin might be a potent therapeutic alternative for liposarcoma patients who have already undergone prior chemotherapeutic treatment.

3. Future direction

3.1. First-line therapies

The efficacy in anti-cancer activity and safety profile of eribulin was fully validated in plenty of preclinical research and clinical studies. After being approved by FDA and marketed as the third-line therapeutic regimen, eribulin is typically utilized for patients with previous treatments. According to a retrospective study published by Fujii et al., patients who had eribulin as their first-line therapy had a decreased incidence of new tumor metastases, raising the possibility that eribulin could be used to stop new metastases in early-phase therapy[31]. Using eribulin as the first line therapy had been largely under-explored domain.

3.2. Treatment for other cancers

Eribulin has shown beneficial in clinical practice for the chemotherapy of diversified classes of breast cancer, including several resistant kinds like the triple-negative breast cancer (TNBC) subtype[32]. Besides, several clinical studies of eribulin on other cancer, including NSCLC, urethral cancer, and cervical cancer prostate cancer, were in process or have been completed[33,34].

3.3. Drug combination

Eribulin is being investigated on drug combination therapies for advanced TNBC in two phase II trials, one with ipatasertib and the other with apatinib and camrelizumab. The investigation of eribulin in combination with nivolumab for the chemotherapy of HER2-negative MBC as well as another combination assay with pembrolizumab for the therapy of HR-positive breast cancer are ongoing. Lenvatinib and pembrolizumab are being used in two studies that combine eribulin with them to treat advanced soft tissue sarcoma, and both are in the phase II stage[33]. It has progressed in several drug combination trials of eribulin.

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3.4. Adverse events

Adverse events in clinical trials have been discussed above. The result of a real-world study on the toxicity of eribulin showed that few severe adverse events were observed in eribulin treatment[35]. Though neutropenia, peripheral neuropathy, as well as fatigue, were reported to be the most frequent adverse reactions, there were only 3.5% of the instances in the study discontinued treatment as the result of severe adverse events, suggesting eribulin was well-tolerated in the treatment of MBC. However, the molecular mechanisms of these adverse events lack in-depth investigation. Further studies on mechanisms might provide evidence to avoid useless toxicity in eribulin treatment.

4. Conclusion

As a novel small-molecule microtubule inhibitor, eribulin exhibits potent anti-cancer efficacy via a unique mechanism involving its inhibitory activity on microtubule dynamics. Numerous clinical trials and real-world research have validated that eribulin is a highly effective and well-tolerated drug for the treatment of solid tumors, particularly for metastatic breast cancer. After receiving FDA approval, eribulin was widely used as a medication for MBC and LPS patients who had already undergone chemotherapy treatment to increase their survival time and quality of life. With further studies being conducted, eribulin is anticipated to have a greater impact on cancer treatment.

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