

ADVANCES IN ONCOLOGY

Current Developments in the Management of Solid Tumor Malignancies

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Nontaxane Microtubule Dynamics Inhibitors

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H&O What is the mechanism of action of nontaxane microtubule inhibitors?

JC The mechanism of action of nontaxane microtubule inhibitors is quite interesting. This class of drugs blocks the mechanism of tubulin's interaction with a cell, making it nonfunctional, and also sequesters some units of the tubulin into what is called *tubulin* and *eribulin aggregates*. These aggregates are known to be toxic to the tumor cell. Eribulin (Halaven, Eisai) is a synthetic analogue of halichondrin B, which is a nontaxane microtubule dynamics inhibitor that was extracted from the marine sponge *Halichondria okadai*.

H&O On what basis did eribulin receive approval from the US Food and Drug Administration?

JC To our knowledge, after anthracycline- and taxane-based therapy in metastatic breast cancer, we do not have a single agent that has increased survival. Positive efficacy results in phase II trials of eribulin led to a phase III study (EMBRACE; Eisai Metastatic Breast Cancer Study Assessing Physician's Choice Versus Eribulin E7389) that compared standard of care to eribulin. In this study, eribulin met the primary endpoint of overall survival and showed a benefit over standard of care.

H&O Can you discuss the EMBRACE study?

JC The EMBRACE study was an open-label, randomized, phase III trial evaluating eribulin versus standard

of care, which was physician's choice of treatment, in patients with locally recurrent or metastatic breast cancer who had been treated with at least 2 prior lines of chemotherapy in the metastatic setting. Patients were randomized 2:1 to receive either 1.4 mg/m² intravenous eribulin on days 1 and 8 of a 21-day cycle or treatment of physician's choice. Patients had to have a good performance status, and it is important to note that patients were enrolled regardless of human epidermal growth factor receptor-2 status.

Study findings showed that patients treated with eribulin reported a better overall survival compared to those who received physician's choice of treatment (hazard ratio, 0.81; median overall survival, 13.2 vs 10.65 months; $P=.04$). Eribulin also had a statistically significant improvement in overall response rate compared to physician's choice of treatment. Interestingly, time to disease progression according to the investigators was also improved, but according to independent review, it did not reach statistical significance. Eribulin was very well tolerated, with a few patients experiencing grade 3 neurotoxicity and grade 3 asthenia, as well as some other adverse events.

H&O Does the intravenous dosing cause any challenges to drug administration?

JC Although eribulin is administered intravenously, the infusion time is very short, lasting only 2–5 minutes. Therefore, although the patient is unable to self-administer eribulin, the duration of infusion is very short. Of

note is that patients do not need prophylactic medication, like antiemetics or corticosteroids, prior to eribulin administration.

H&O What do the findings from the EMBRACE trial mean for women with metastatic breast cancer?

JC There are very limited treatment options for women with extensively pretreated metastatic breast cancer, so I think this is very good news for patients with aggressive disease. In patients who do not have a curative treatment, this is another opportunity to prolong survival with a good quality of life. In my opinion, after trastuzumab (Herceptin, Genentech), this is one of the most important discoveries in metastatic breast cancer in the last decade.

H&O Are there any ongoing studies of eribulin?

JC There is a randomized phase III trial, which is comparing eribulin versus capecitabine in patients who received between 1 and 3 prior chemotherapy lines (E7389-G000-301). We expect results some time this year. This study has primary endpoints of time to disease progression and overall survival. Eisai is conducting various studies of single-agent eribulin as well as combinations of eribulin and trastuzumab in metastatic breast cancer patients. These studies are currently recruiting patients.

H&O What is the future for eribulin?

JC Eisai has received a positive opinion for the use of eribulin from the Committee for Medicinal Products for Human Use, which is the scientific committee of the European Medicines Agency (EMA). The committee's submission was supported by the results from the EMBRACE trial. Also, the National Institute for Health and Clinical Excellence (NICE) has recommended that eribulin be given a priority review under its single technology appraisal process. It appears that both NICE and the EMA are excited about eribulin's survival benefit in metastatic breast cancer, and we hope to see eribulin approved in Europe this year. With the ongoing studies, we hope to gain more information on eribulin in the first-line setting and in combination with other agents. In the next few years, we will be able to determine the role of eribulin in the treatment of other tumors.

Suggested Readings

Cortes J, Vahdat L, Blum JL, et al. Phase II study of the halichondrin B analog eribulin mesylate in patients with locally advanced or metastatic breast cancer previously treated with an anthracycline, a taxane, and capecitabine. *J Clin Oncol*. 2010;28:3922-3928.

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Smith JA, Jordan MA. Determination of drug binding to microtubules in vitro. *Methods Cell Biol*. 2010;95:289-299.