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Evaluation of the use of oral care to prevent oral mucositis in estrogen receptor-positive metastatic breast cancer patients treated with everolimus: A phase III randomized control trial

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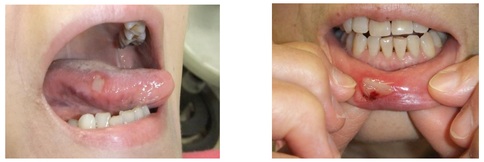
Background

- In the randomized phase III study (BOLERO-2 study) among patients with estrogen receptor (ER)-positive advanced breast cancer, the progression-free survival in the everolimus plus exemestane group was significantly longer compared with the exemestane monotherapy group.[1]
- As an adverse drug reaction to everolimus, all-grade oral mucositis was reported in 58% of all patients and 81% of Asian patients.[1,2]
- Development of oral mucositis can significantly affect treatment adherence.
- Oral mucositis can also result in postponement of a change in treatment, discontinuation of treatment, and prolongation of hospitalization.
- An effective prophylactic treatment for oral mucositis was not established.
- Consequently, oral management is important for preventing both oral mucositis and exacerbation of oral mucositis.
- Appropriate oral care prevents oral mucositis as an adverse drug reaction to AC therapy for breast cancer. Oral care consisted of tooth surface cleaning and scaling weekly. [3]
- The data indicate that stomatitis in advanced breast cancer patients tends to develop within the first month of therapy with everolimus.

Figure 1: Clinical characteristics of everolimus-associated oral mucositis



Images courtesy of Yoshihide Ota M.D., Tokai University

<References>

1. Baselga J, et al. N Engl J Med 2012; 366: 520-529.
2. Noguchi S, et al. Breast Cancer 2013.
3. Saito H, et al. Support Care Cancer 2014; 22: 2935-2940.

Objectives

To examine whether the occurrence of oral mucositis can be reduced by appropriate oral management in patients after instruction from dental or oral surgeons provided to an observation group in a randomized, controlled study of women undergoing treatment with everolimus for estrogen receptor-positive (ER+), hormone therapy-resistant refractory breast cancer.

Methods

Study design

- This is a randomized, multi-center, open-label, phase III study evaluating the efficacy of dental oral care to prevent oral mucositis induced by everolimus in postmenopausal women with ER+ advanced breast cancer who have been prescribed oral everolimus (10 mg daily) plus exemestane (25 mg daily).
- Patients were randomized in a 1:1 ratio to the professional oral health care group and the control group.

Eligibility criteria

- Postmenopausal women with hormone receptor-positive (HR+) metastatic breast cancer
- Resistance to aromatase inhibitor therapy
- No more than one prior chemotherapy treatment (anti-neoplastic drugs) since the diagnosis of metastatic or recurrent breast cancer

Study endpoints and analyses

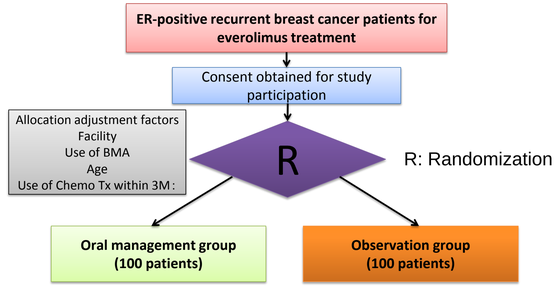
Primary endpoint:

- **Incidence of all-grade oral mucositis (CTCAE ver3.0) after everolimus treatment (evaluated by an oncologist)**

Secondary endpoints

- Incidence of each grade of oral mucositis (evaluated by an oncologist)
- Incidence of all grade oral mucositis (evaluated by a dental or oral surgeon)
- Time to onset of oral mucositis
- Duration of each grade of oral mucositis
- Health-related quality of life (HRQOL)
- Time to treatment failure (TTF)

Study design



BMA: bone modifying agents

Protocol treatment

D group (Oral management)
Scaling and crown polishing weekly, brushing instruction, tongue plaque removal instruction, gargling instruction (Neostelin Green 0.2% mouthwash solution), and dexaltin ointment use when grade 1 oral mucositis occurs.

Observation group (brushing instruction only group)
Gargling instruction (normal saline), brushing instruction, use of oral mucositis ointment prohibited until the appearance of Grade 2 oral mucositis

* Duration of oral management protocol treatment is 8 weeks in both groups.

- Scaling and crown polishing: Dental calculus will be removed with a specialized scaler once weekly, and a specialized tool will be used to polish the dental crown to make it more difficult for bacteria to adhere.
- Brushing instruction: Instructions given to perform cleaning with a tooth brush, interdental brush, dental floss and the like after every meal.
- Tongue plaque removal instruction: Instructions given to remove tongue plaque after brushing.
- Oral management group, gargling instruction: Instructions given to gargle with Neostelin Green 0.2% mouthwash solution (benzothonium chloride-based) after brushing and tongue plaque removal.
- Brushing instruction only group, gargling instruction: Instruction-given to gargle with physiological saline after brushing and tongue plaque removal.

CTCAE (ver 3.0):

Adverse Event	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Stomatitis (clinical examination)	Erythema of the mucosa	Patchy ulcerations or pseudomembranes	Confluent ulcerations or pseudomembranes; bleeding with minor trauma	Tissue necrosis; significant spontaneous bleeding; life-threatening consequences	Death
Stomatitis (functional/ symptomatic)	Minimal symptoms, normal diet; minimal respiratory symptoms but not interfering with function	Symptomatic but can eat and swallow a modified diet; respiratory symptoms interfering with function but not interfering with ADL	Symptomatic and unable to adequately aliment or hydrate orally; respiratory symptoms	Symptoms associated with life-threatening consequences	Death

Safety monitoring

- All adverse events (AEs) without oral mucositis will be assessed according to the Common Terminology Criteria for Adverse Events (CTCAE) version 4.0.
- To ensure patient safety, all serious AEs will be reported, regardless of suspected causality, after the patient signs the informed consent until finished with the 8 weeks protocol.

Statistical assumptions and patient recruitment

- The incidence of all grades of oral mucositis in Asian subjects in the BOLERO-2 study was 80%, and the incidence of all grades of oral mucositis upon everolimus administration in Japanese subjects will be assumed to be 80%. The implementation of oral management will be assumed to reduce the relative risk by 25%, and for a two-sided α-level of 5% and statistical power of 80% with Fisher's test the necessary sample size in the two groups is 182. Taking subject exclusions into account, the target sample size was set at 200.
- Scheduled number of enrolled patients: D group: 100 subjects, B group: 100 subjects, 200 subjects in total
- Enrollment period: Two years from first patient enrollment

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