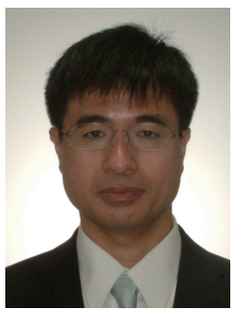
INTER-ETHNIC VARIATION IN THE PHARMACODYNAMIC PARAMETERS OF AROMATASE INHIBITORS: A RETROSPECTIVE OBSERVATIONAL STUDY


Hiroshi Ishiguro

Hiroshi Ishiguro[1], Masakazu Toi[2]

[1]*Outpatient Oncology Unit, Kyoto University Hospital, Japan,*
[2]*Department of Breast Surgery, Kyoto University Hospital*

There are considerable inter-ethnic, inter-patient, and even intra-patient variations in the absorption, excretion and metabolism of drugs. The main causes of these large pharmacokinetic variations are (i) polymorphism in the genes encoding drug-metabolizing enzymes or transporter proteins, and (ii) external factors such as concomitant medications and diet. Ideally, if the information is available, drug dose should be based on pharmacodynamic parameters, for example warfarin dose is adjusted according to INR value. However, this approach is not possible for most anti-neoplastic drugs, despite it being widely acknowledged that a single recommended drug dose is not ideal in the face of highly variable pharmacokinetic and pharmacodynamic profiles. If it is possible to base dosing strategies on pharmacokinetic and pharmacodynamic data, better outcomes in terms of cancer recurrence and progression can be achieved, with an improved safety profile.

In some cases, occurrence of a specific side-effect can be used to predict the likelihood of treatment success. A good example is the occurrence of acneiform skin rash during treatment with epidermal growth factor receptor antibodies (e.g., cetuximab and panitumumab). Similarly, with the kinase inhibitors gefitinib and erlotinib, skin toxicity is associated with a higher probability of treatment response. For tamoxifen, there is some evidence that women who develop vasomotor symptoms have a lower risk of breast cancer recurrence than those who do not. For aromatase inhibitors (AIs), the appearance of new vasomotor symptoms or joint symptoms within the first 3 months of treatment is a useful biomarker, indicating a greater likelihood of responding to endocrine treatment. When administered to postmenopausal women, AIs act to inhibit aromatase from converting androgens to estrogens, and third-generation AIs are now used for treatment of metastatic breast carcinoma as well as for adjuvant treatment of operable breast cancer. Currently, AIs are indicated for breast cancer patients who are postmenopausal and have a positive hormone-receptor status. There is much evidence that estrogen or progesterone receptor-positive breast carcinomas respond better to tamoxifen and AIs. A recent review concluded that for patients with metastatic breast cancer treated with anastrozole or letrozole (both potent and well-tolerated third-generation nonsteroidal AIs) as first-line therapy, a positive hormone-receptor status has a strong relationship with increased time to disease progression. However, the clinical relevance of hormone receptors when using AIs is only moderate because approximately only 30% of patients exhibit an objective clinical response and, therefore, the power to discriminate between responding and non-responding patients is low. There are intensive efforts underway to find other biomarkers that could help with predicting the clinical efficacy of AIs.

A number of in vitro studies have indicated that letrozole is more effective than anastrozole at reducing aromatization. In a large, well-designed study, Dixon et al. compared the effects of adjuvant anastrozole and letrozole on circulating E2 and E1S levels in postmenopausal women with breast cancer. They found that letrozole

reduces plasma E2 and E1S levels to a significantly greater extent than does anastrozole in postmenopausal women with hormone receptor-positive breast cancer. However, it remains unclear whether the difference between letrozole and anastrozole in terms of aromatase inhibition is clinically significant. Clinical trials may have been carried out to compare AIs with respect to levels of pharmacodynamic markers such as E2; but the results of that trial are not yet available. The limited availability of assays for measuring low concentrations of E2 is also a barrier to further understanding the relative benefits of various AIs. Estradiol is the major active hormone binding to the estrogen receptor in breast cancer cells, and even at low concentrations (e.g., 1 pmol/L-1 nmol/L) it can stimulate tumor growth.

We have personally experienced several patients who experienced no reduction in estradiol levels after AI treatment. We hypothesize that a lack of estradiol response to AI therapy might serve as a negative predictive marker for hormone treatment response. By combining estradiol response with other clinical predictive factors, such as vasomotor and joint symptoms, it might be possible to develop a new predictive model for hormone treatment response. We report here the results of a retrospective observational study regarding the relationship between drug efficacy and pharmacodynamic parameters (e.g., side-effect profile and plasma estrogen level) among patients being treated with AIs for breast cancer. We studied patients with metastatic disease and those with operable disease who received adjuvant endocrine treatment. The subjects of the study were Asian patients with various ethnic backgrounds.