SIDE EFFECTS OF LONG-TERM USE OF AROMATASE INHIBITORS

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Aromatase inhibitors (AI) have proven effective drugs in the treatment of breast cancer during the postmenopausal period. In recent years, they are in the top line of the complex medical treatment of hormone-positive tumors of various prevalence and stage of disease. It should be noted that currently used in practice solely AI third generation (letrozole, anastrozole and exemestane) as earlier design allowed a significant number of serious side effects. At the same time over the past few years, a growing number of clinical publications in which there is a serious discrepancy between the accumulated data from controlled clinical trials on the safety profile of these drugs with the data obtained from medical practice. It should be remembered that AI often take elderly patients who have a variety of comorbidities, therefore, the presence of additional adverse effects associated with taking any medication, should be reduced to a minimum level.

The aim of our study was to evaluate the nature and frequency of side effects long-term use of AI and their possible prevention according to clinical trials and literature data.

Materials and Methods: We analyzed data from clinical trials available results at the beginning of 2015 (5198 study). This included testing of exemestane (159), anastrozole (228) and letrozole (273). In addition, analyzed the available literature on AI side effects and effectiveness of the methods to prevent them.

Results: The most frequent side effects of AI were increasing the frequency and intensity of hot flashes, joint pain of varying severity, weakness, mood changes, sore throat, dyspepsia and vomiting, depression, high blood pressure, osteoporosis, swelling of extremities and headache. Moreover, the intensity and frequency of most of them increased respectively terms of reception of AI. For example, if after two years of taking the drugs serious difficulties due to the side effects observed approximately 10% of the patients, after 3 years were not less than one third.

Analysis of the data revealed significant differences in the defined frequency and spectrum of side effects during clinical trials and clinical publications on the topic. For example, in clinical trials the frequency of arthralgia and myalgia varying intensity observed in 15-21.8% of patients. At the same time, practical publications

indicate the level of comparable intensity of symptoms in 35-58.5% and even 63.9% of the patients. In addition, half refused to taking the AI patients (50.4%) did so because of the severity of pain. But in general, failure rates is, according to various estimates, from 27.8 to 36% of patients. It is interesting that in pilot clinical trials of the last century, these effects were recorded in only 5% of patients. As the therapeutic methods of arthralgia and myalgia, indicate certain (albeit modest) positive effect of the reception of ibuprofen, the use of physical therapy, massage and acupuncture. At the same time, increase the risk of fractures is reliably prevented parallel use of bisphosphonates and denosumab (Prolia) reception.

If the frequency is fixed by clinical trials and clinical publications side effects comparable with regard to the development of dry mucous membranes (3-7.2%), osteoporosis (2.7-10%), the intensification of hot flashes (25-33%) and general weakness (18-24.1%), the effects of a number of other effects, there is considerable differences again. In particular, it concerns the increase in anxiety and depression (clinical trials - about 1.5%, and clinical publications - 14-17%), memory impairment (respectively, 2% and 48%). Furthermore, clinical trial data taken into account when receiving AI only a limited number of side effects. At the same time outside of the results is a significant number of them quite significant, because of which many patients are forced to refuse treatment. Among these side effects: a significant decrease in libido - up to 24%, sleep disorders - to 53.4%, increased sweating - 16,4-17%, diarrhea - 9-12%, vaginal bleeding - 3.8%, and so on. In particular, after two years of receiving AI observed, although relatively rare, and other significant side effects, such as "dry eye syndrome" (3%), "carpal tunnel syndrome" (1.5%), numbness of fingers extremities (1.2%) and some other.

Conclusions: It was found significant differences in the incidence of side effects is determined during chronic administration of AI during clinical trials and clinical publications. Apparently, they were associated with the peculiarities of design and selection of patients when preparing for the clinical trials, when the inclusion criteria included a limited number of comorbidities, and the refusal of treatment (including due to the severity of adverse symptoms) patients were excluded from the calculation obtained results. Inclusion in the number of dropouts due to side effects of the course of clinical trials would increase the incidence of side effects in two or three times. Most likely, the perform clinical trials sponsored by the manufacturer of medication of is not ideal to obtain objective results.