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EDITORIAL

Desescalation in Aromatase Inhibitors prescription for menopausal women with positive hormonal receptors breast cancers

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Introduction.

The use of aromatase inhibitors (AI) is widely accepted in positive hormonal receptors breast cancers. However a significant proportion of patient complain for side effects leading to abandon the treatment. Since the effect of AI is mainly based on the decrease of serum estradiol, the question of dose adaptation in decreasing the dosage of IA while keeping its biological effect was raised.

Recent papers brought major contribution in this field and we present here an analysis of some of these recent data validating the reduction of AI prescription without harm for the patient.

A significant proportion of post-menopausal women treated for a positive hormonal receptors breast cancer treated with IA reports side effects, mainly bone pain, but also osteoporosis, hot flushes, increase of cholesterol which can after months or years drive to a cessation the recommended 5-10 years of treatment and consequently expose to a survival risk.⁽¹⁾

AI prescription is reserved to post-menopausal women and breast cancers are diagnosed in more than 20% of women over 70 years old, who can already have arthritis problem. Ageing is associated with a decreased drug clearance resulting in an increase exposure to the drug, reflected by increased AUC's.

We reported in 2015⁽²⁾ a proof of concept recommending an intermittent dosage giving the drug every other day, in order to avoid the abandonment of the drug reported by 30-40% of the patients⁽²⁾ we suggested that giving one pill every otherday could be an opportunity since the IA half-life is 72 hours and the biological efficient dose was every other day, especially in older patients. During presentations in meetings specialists in prevention were very interested and discuss with us this opportunity. From the fifties the population experience a reduction in muscle mass, decrease of body water and an increase in fat tissues, leading to a modification in the distribution of the drugs. Hydrophilic drugs and accumulation of lipophilic drugs is a result of these changes Hepatic function decrease, without changes in the histology but the hepatic blood flow decrease (50% at the age of 70). The liver weight and size decrease enzyme activity, which is the case with IA.

Modifications in the Gastric pH due to the frequent interactions with other medications can also modify the absorption of IA.⁽³⁻⁵⁾

A recent paper published in the JAMA⁽⁴⁾ reported the oestradiol blood dosage in a 6-8 weeks neo adjuvant hormonal therapy non inferiority randomized trial, before surgery, comparing prescription of AI, daily, 3 times a week and once a week.

Oestradiol decreased from 89% in the daily prescription, 86% in the three time a week group and 61% once a week. The difference was statistically different between Daily-Three time a week compared to once a week

Obviously the authors suggested a reduction of the dose for most patients, under a regular control of serum estradiol. Their recommendation was to realize a larger prospective randomized trial on a larger number of patients during a longer follow up.

Additional information was given more recently in the prevention study from the Cuzik paper⁽⁵⁾ in the Lancet oncology in which High risk breast cancer patients were randomly assigned either to anastrozole treatment vs placebo. The regular dosage of serum estradiol was related to the remaining estradiol Level. Their recommendation during this 5 years follow up study was to follow regularly the level of serum estradiol.

Reducing the dosage of a drug in ageing patient is not a new concept and fits with common sense.

However de escalation is always a challenge because it often goes against Evidence based Medicine recommendations based on old prospective randomized trials. Reproducing these trials wouldn't be possible. However

following a treatment by a targeted blood marker is an efficient and modern way to judge the treatment efficacy and eventually to adapt the dosage.

Conclusion

The reduction of AI dosage is an efficient way to help the patients to better tolerate the drug, keep its primary effect and to avoid a recurrence and avoid the frequent abandonment of the drug due to its side effects. Longer follow up and blood testing at a regular interval would be recommended during the reduced doses treatment

Conflicts of Interest:

None

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